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*Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico*, 47:305, Aug., 1955.

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Editorial

Pathogenesis of Malignant Hypertension

IN THE usual definition, the benign phase of essential hypertension is characterized by elevated diastolic pressure associated with diffuse vascular disease (arterial and arteriolar sclerosis) of unknown origin but without significant impairment of renal excretory function.

Malignant hypertension has been defined in a variety of ways and there is no complete agreement about its pathognomonic features. The most common definition is that it usually represents an accelerated phase of benign essential hypertension, which was previously existent for a variable period, and that it is characterized by cerebral and ocular signs and symptoms as constant diagnostic features, with death occurring in a short time, usually from terminal renal failure. The recent definition of malignant hypertension, proposed by the Medical Advisory Board of the Council for High Blood Pressure of the American Heart Association, is perhaps a happy compromise, for it reads: "A clinical phase, rarely occurring *de novo*, more often appearing after a primary or secondary hypertension, characterized by diastolic hypertension and by accelerated and progressive renal damage, usually (but not necessarily) accompanied by papilledema, often by retinal hemorrhages and 'exudate,' and giving rise to early death from uremia unless the course is terminated along the way by complicating brain or heart damage." There can be no great quarrel with this definition, even by those who stress the primary pathogenetic importance of the kidney, because there is no reference to the origin of the hypertension.

There is even greater diversity of opinion about the pathogenesis of malignant hypertension than there is about the definition. Some consider it to be a form of essential hypertension, not of renal origin, but marked by renal excretory impairment occurring as a late or terminal manifestation; others (including the writer) believe that the malignant phase, like the benign, is primarily, and even more obviously, of renal origin. There are reasons, clinical, pathologic, and experimental, for this wide difference of view. One source of confusion has been the failure of many investigators to recognize that the pathologic changes of the kidneys in the malignant phase are neither uniform nor unique. Another source of difficulty has been lack of agreement about the nature and pathogenesis of the necrotizing arteriolar lesion that is found in the kidneys and other organs, and that is regarded by most investigators as a pathognomonic feature of malignant hypertension.

Experimental investigations carried out on the rat have contributed to this confusion. In this animal, so-called "necrotizing arteriolitis" has been produced by a variety of means — from injections of desoxycorticosterone acetate and methyl-androstenediol to repeated elevation of the blood pressure produced by intravenous injections of pitressin or by sudden injections of Ringer's solution directly into the systemic arterial stream. The fact is, however, that the rat is unusually susceptible to periarteritis nodosa, which usually involves arterial branches larger than the arterioles, and most investigators, unfortunately, have misinterpreted periarteritis nodosa as equivalent to, or identical with, arteriolar necrosis. To what extent the incidence and severity of spontaneous lesions may have been increased by these experimental procedures is not germane

to this subject—the important fact is that the lesions represent periarteritis nodosa and not arteriolar sclerosis or necrosis, the characteristic lesions of essential hypertension.

In the dog, in which both the benign and malignant phases of human essential hypertension were first reproduced, periarteritis nodosa rarely occurs under natural conditions and does not complicate the microscopic picture in the hypertensive animal. In the dog, also, the necrotizing arteriolar lesions are the exact counterpart of the lesions found in malignant hypertension in man, and, as in man, accompany impaired renal function. Arteriolar necrosis has also been observed in bilaterally nephrectomized, "treated" dogs, with hypertension and azotemia (but not in untreated animals). The dog, and not the rat, should therefore be the animal of choice for investigations of the future dealing with the elucidation of the pathogenesis of arteriolar necrosis.

A common, but erroneous, belief is that arteriolar necrosis (with fibrinoid degeneration and with or without some perivascular inflammation), which is pathognomonic of malignant hypertension, represents an accelerated form of arteriolar sclerosis. There is no morphologic or pathogenetic basis for the confusion of this lesion with arteriolar sclerosis. There is no better reason for regarding arteriolar necrosis as accelerated arteriolar sclerosis than there is for considering the fibrinoid necrosis of periarteritis nodosa as an accelerated form of arterial sclerosis, even though it may be difficult, at times, to differentiate the healed (or terminal) stage of panvasculitis from arterial sclerosis.

Another common belief is that arteriolar necrosis is so diffuse and so severe in the kidneys that it is actually the *cause* of the renal failure. The development of widespread arteriolar necrosis throughout the body has even been referred to by one investigator as a "conflagration." There is no basis for such a statement. As a result of a study of many kidneys and other organs from patients in the malignant phase of essential hypertension who had pronounced renal insufficiency, many of whom had died in uremia, I have found that in some the number of intrarenal necrotic arterioles was small. As a result of this study and of investigations dealing with experimental renal hypertension produced by constriction of the main renal arteries, I have come to regard the arteriolar necrosis as merely a rapidly developing, sporadic, variable, secondary, and usually terminal, manifestation of the malignant (accelerated) phase of essential hypertension.

Exactly what it is that brings about the fibrinoid necrosis of previously normal or sclerotic arterioles is not yet known. The old view that it is the result of intense vasospasm is certainly not tenable, because spasm as intense and much more prolonged occurs in the benign phase without resulting in arteriolar necrosis. Perhaps the best evidence for the view that the arteriolar necrosis of the malignant phase, though pathognomonic, is not of primary pathogenetic significance, insofar as both the hypertension and the renal insufficiency are concerned, is that it has been observed to develop in 2 or 3 days in many organs of dogs with previously normal blood vessels, but with experimental hypertension and renal insufficiency produced by excessive constriction of both main renal arteries. In these animals the hypertension and the impairment of the excretory function begin early and the development of the wide-spread necrotizing arteriolar lesions usually occurs in the terminal stage, when the animal is in convulsive uremia. It should be obvious, therefore, that in this type of experimental hypertension, which mimics in every way the malignant phase of essential hypertension, the necrotizing arteriolar lesions play no part in the pathogenesis of either the hypertension or the renal insufficiency, and are merely a consequence of both. The probability is great, therefore, that the same holds true for the malignant phase of hypertension in man.

In my opinion, excretory failure is not caused by the arteriolar necrosis but by obliterative arterial and arteriolar sclerosis of unusually great degree or by one of several complicating renal pathologic conditions the occurrence of which brings about the impairment of renal function and the development of the necrotizing arteriolar lesions. The most common of these renal complications, the importance of which has not been sufficiently

stressed, because it is an insidious disease and frequently overlooked clinically, is chronic interstitial nephritis (pyelonephritis) which, when sufficiently severe, brings about the excretory failure of kidneys previously the seat of only arterial and arteriolar sclerosis and determines the development of the malignant phase. The other complicating renal diseases which may have the same effect are glomerulosclerosis and various types of glomerulonephritis, which, when superimposed upon renal arterial and arteriolar sclerosis, of even moderate degree, may precipitate the change from the benign to the malignant phase. Interstitial nephritis (pyelonephritis), however, does this far more frequently; and some of the histologic features of the kidneys, such as the focal glomerulitis and the proliferative endarterial fibrosis and elastosis of vessels larger than arterioles, frequently regarded as specific for malignant nephrosclerosis, are really characteristics of the chronic pyelonephritis that helps to bring about the accelerated hypertension. Less commonly, the malignant phase occurs as a result of the development of arteriolar sclerosis or periarteritis nodosa in an individual with a previously existent chronic bilateral pyelonephritis and its accompanying glomerular and vascular disease.

The importance of the part played by interstitial nephritis as one of the possible causes of malignant hypertension cannot be stressed too greatly because it promises possible treatment, and even prevention, of the most common pathologic condition responsible for bringing about the change from the benign to the malignant phase of essential hypertension.

HARRY GOLDBLATT

As the student, fresh from the schools, and proud of his supposed superiority in the refinements of diagnosis, advances into the stern realities of practice, he will be taught greater modesty and a more wholesome caution: he will find, especially in chronic disease, that important changes may exist without corresponding physical signs,—that as disease advances, its original special evidences may disappear,—that the signs of a recent and trivial affection at one portion of the heart may altogether obscure or prevent those of a disease longer in standing and much more important,—that functional alteration may not only cause the signs of organic lesion to vary infinitely, but even to wholly disappear,—that the signs on which he has formed his opinion to-day may be wanting to-morrow,—and lastly, that to settle the simple question between the existence of functional and that of organic disease will occasionally baffle the powers of even the most enlightened and experienced physician.—WILLIAM STOKES. *The Diseases of the Heart and the Aorta.* Dublin, 1854.

The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life

I. Prognosis with Special Reference to Survivorship

By MAY G. WILSON, M.D., AND WAN NGO LIM, M.D.

The object of this study is to provide information on the natural course of rheumatic heart disease in the third, fourth, and fifth decades of life. It is concerned with 757 out of 1,042 children under observation during the years 1916 to 1956 who reached the age of 20 or more years. The major manifestations of rheumatic fever experienced by these patients from the onset of the disease is related to the degree of residual cardiac damage. Survival to successive ages was analyzed with respect to sex, type of valvular lesion, and degree of cardiac enlargement.

BASIC data on the natural course of a chronic disease are essential for evaluation of the effect of therapeutic procedures. In 1947 we presented the mortality experience of a group of 1,042 children who had been under medical supervision during the years 1916 to 1947.[1] Another 10 years have elapsed, providing information on the natural course of rheumatic heart disease in the third, fourth, and fifth decades of life. This report is concerned with 757 of those patients who have reached the age of 20 years or more. Prognosis will be considered in terms of the major manifestations of rheumatic fever experienced during the course of the disease and the degree of residual cardiac damage.[1, 2] Survivorship will be analyzed to successive ages, specific for sex, type of valvular lesion, and degree of cardiac enlargement.

In order to assess survivorship or mortality risks for any of these groups, due account must be taken of the duration of follow-up for the different individuals entering the study. This has been done by the actuarial methods used by life insurance companies, which are applicable to studies on prognosis.[3, 4] The data thus give a partial description of the natural history of the disease, and have relevance to the selection of patients for cardiac surgery or other therapeutic procedures.

In interpreting the data it must be remembered that our patients represent a group that sought medical care in childhood and have been followed without further selection into adult life. They are not therefore comparable to a group of adults in whom cardiovascular disease is discovered on examination or to those seeking medical care for cardiopulmonary symptoms.

Sufficient data have accumulated in the past 8 years to indicate that immediate surgical mortality has decreased with experience, both in surgical technics and in selection of patients, and the majority of published studies indicate an improvement in functional cardiac status[5-8] but beyond this we have no real assessment of results. The difficulty in judging the surgical experience as reported in the literature is that survivorship is usually given in terms of the direct calculation of the proportion of patients in any series who survived, without any account being taken of the variable length of follow-up. This index cannot be interpreted even in a descriptive sense.

It is hoped that the present study will give further perspective on the disease and furnish some guides in the selection of patients for surgical intervention as well as for evaluating its effect on longevity.

MATERIAL

From an original total of 1,042 children with rheumatic heart disease who came under observe-

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tion since 1916, the records of 757 patients who reached the age of 20 or more years were reviewed.[1] Of these, 73, or 10 per cent, were lost at various points in the follow-up; 90 per cent were observed until death or the end of the study on January 1, 1956.

The character of the sample and type of medical supervision have been described in our 1947 study, and characterize the entire 40-year period of study from 1916 to 1956. A diagnosis of rheumatic fever was only made on the following major manifestations: carditis, polyarthritis, chorea, or subcutaneous nodules. It needs to be emphasized that all of the patients demonstrated cardiac involvement. Patients with symptoms suggestive of rheumatic fever, without cardiac involvement, were not included in this study. Subacute carditis was characterized by poor heart sounds, tachycardia or gallop, increasing cardiac chamber enlargement demonstrable on fluoroscopic examination with or without new and changing murmurs, and electrocardiographic evidence of myocardial involvement. Acute carditis was characterized by the above findings and pericardial rub, diminishing cardiac reserve, dyspnea, and symptoms and signs of congestive failure.

The sex distribution and the age at last observation or death are presented in table 1. It will be noted that there are about 100 more females than males. About three fifths of the total of 757 patients have been followed beyond 30 years of age, about one third beyond 35 years, and one seventh beyond 40 years of age.

The number of deaths according to causes and age groups are summarized in table 2. During the period of observation, 78 patients died who had reached the age of 20 or more years. Of these, 53, or 68 per cent, of the deaths were attributed to rheumatic heart disease; 8 or 10 per cent, to bacterial endocarditis; and 17, or 22 per cent, to other diseases or accidents. Verification of the cause of death was obtained by postmortem examination in 25 patients, or 33 per cent.

Criteria for diagnosis followed the nomenclature and criteria of the New York Heart Association.[9] The cardiac diagnosis at the last observation is presented in table 3. The diagnosis of mitral insufficiency, mitral stenosis, and aortic insufficiency was made on the basis of characteristic constant murmurs and cardiac chamber enlargement that persisted at least 6 months to 1 year after termination of active carditis. Murmurs were considered to have regressed if they became inconstant or uncharacteristic for a period of 1 year or more. The diagnosis was not changed when murmurs regressed and enlargement of cardiac chambers and characteristic heart sounds remained. Patients with auscultatory murmurs of valvular lesions were separated into those whose murmur was "constant" or "regressed," i.e., MI^1 or MI^2, etc. during the period of observation.

TABLE 1.—*Distribution of Patients Who Were Followed to Age 20 or Beyond, by Sex and Age at Last Observation*

Age (years)	Female	Male	Total patients	
			Number	Per cent
20–25	66	42	108	14
25–30	104	83	187	25
30–35	104	113	217	29
35–40	80	55	135	18
40–45	51	25	76	10
45–52	25	9	34	4
Total	430	327	757	100

TABLE 2.—*Age Distribution of Patients at Last Observation and of Deaths, by Cause*

Age at last observation (years)	Number of patients	Total deaths	Number of deaths			
			Cardiac causes		Noncardiac causes	
			Rheumatic heart disease	Bacterial endocarditis	Other	Accident
20–25	108	28	16	4	3	5
25–30	187	17	10	3	2	2
30–35	217	16	13	0	1	2
35–40	135	13	10	1	1	1
40–45	76	1	1	0	0	0
45–52	34	3	3	0	0	0
Total	757	78	53	8	7	10

Cardiac chamber enlargement was determined by serial fluoroscopic examination in the posteroanterior and right anterior oblique positions with contrast medium, and in the left anterior oblique position at standard degrees of rotation on a turntable.[10-12] Patients were classified as having "moderately" enlarged hearts (1+ or 2+) who usually showed no abnormality of cardiac silhouette or increased cardiothoracic ratios in the posteroanterior view. In the left anterior oblique position the normal angle of clearance of the left ventricle of 45 or 50 degrees was increased to 55 or 60 degrees, and in the right anterior oblique position there was 1+ displacement of the esophagus by an enlarged left atrium. Patients were considered to have "markedly" enlarged hearts (3+ or 4+) whose abnormal cardiac silhouette was usually discernible in the posteroanterior view, frequently showing an increase in cardiothoracic ratio. In the left anterior oblique position the angle of clearance of the left ventricle was increased to 65 to 90 degrees, and in the right anterior oblique position retrodisplacement of the barium-filled esophagus by the

TABLE 3.—*Cardiac Diagnosis at Last Observation or Death*

Age group (yr.)	Patients		Valvular deformity*						Degree of chamber enlargement				Functional classification				Atrial fibrillation		Bacterial endocarditis	
			MI		MS		AI		1 to 2+		3 to 4+		I		II to IV					
	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead	Living	Dead
20–25	80	28	53	7	21	10	6	11	72	12	8	16	78	12	2	16	1	1	1	4
25–30	170	17	109	2	51	7	10	8	154	7	16	10	168	6	2	11	0	1	2	3
30–35	201	16	128	2	59	5	14	9	185	4	16	12	195	3	6	13	4	6	0	0
35–40	122	13	58	1	54	4	10	8	109	3	13	10	115	3	7	10	2	6	2	1
40–45	75	1	23	0	39	1	13	0	60	0	15	1	69	0	6	1	3	0	0	0
45–52	31	3	9	0	16	2	6	1	26	0	5	3	25	0	6	3	3	2	0	0
Total...	679	78	380	12	240	29	59	37	606	26	73	52	650	24	29	54	13	16	5	8

In this and subsequent tables and graphs: MI = mitral insufficiency alone, MS = mitral stenosis (includes mitral insufficiency), AI = aortic insufficiency (includes mitral and aortic lesions), 1 to 2+ = "moderate" cardiac chamber enlargement, 3 to 4+ = "marked" cardiac chamber enlargement.

* Diagnosis was not changed when the murmur regressed.

left atrium was 2+ to 4+. Abnormalities of the cardiac silhouette in all positions were duly noted.

Vital capacity measurements were recorded at each clinic visit. Serial electrocardiographic tracings, including precordial leads, were obtained on all patients during the latter years of the observation period.

METHODOLOGY

Analysis of long-term follow-up observations is best expressed in terms of a life table or its equivalent. The requisites for deriving a life table include a specified starting point and the distribution according to time from the starting point of the number of individuals alive and under study, the number lost from observation, and the number of individuals who died. In this study, patients had as their starting point 20 years of age. In analyzing survivorship, the information furnished by each individual in the study must be included for the entire period of observation. The assumption in handling the "lost" patients is that subsequent to their last observation they are dying off at the same rate as those remaining under follow-up. It is important to note that the 73 patients who were lost from observation at various points in our follow-up were slightly more favorable in their diagnostic classification than those remaining under follow-up. It seems unlikely, therefore, that any appreciable number were lost because they died or that the assumption as to subsequent mortality is seriously in error.

As in our previous analysis, we have presented both the average annual death rate for 5-year age groups and the probability of dying between the birthdays that mark the beginning and close of each 5-year period for all cases. The latter description permits the calculation of a survivorship table from the age of 20 years to the latest age to which the patients have been followed. We have presented this survivorship only to the age of 45 years, since, up to the present time, only a small number have attained later ages and the sampling errors therefore became substantial.

The survivorship figures were obtained through a conventional life table method, computed for each year of life. A comprehensive description and discussion of such methods has been presented by Merrell.[13]

CLINICAL COURSE AND DEGREE OF RESIDUAL CARDIAC DAMAGE

During the 40-year period of observation for the total of 757 patients, acute carditis with or without subacute carditis occurred in one or more attacks in one third of the group, while one or more attacks of subacute carditis occurred in two thirds. Of the associated major manifestations polyarthritis occurred in one or more attacks in one third of the patients, chorea in another third, and polyarthritis and chorea in about one sixth. Carditis was associated with only minor manifestations in about one fifth of the patients. Only 3 per cent experienced an attack of rheumatic fever after the age of 20 years.

A comparison of the relative incidence of the major manifestations of rheumatic fever experienced by 757 patients during the course of the disease, according to cardiac diagnosis at last observation, is presented graphically in figure 1. It will be noted that for 392 patients

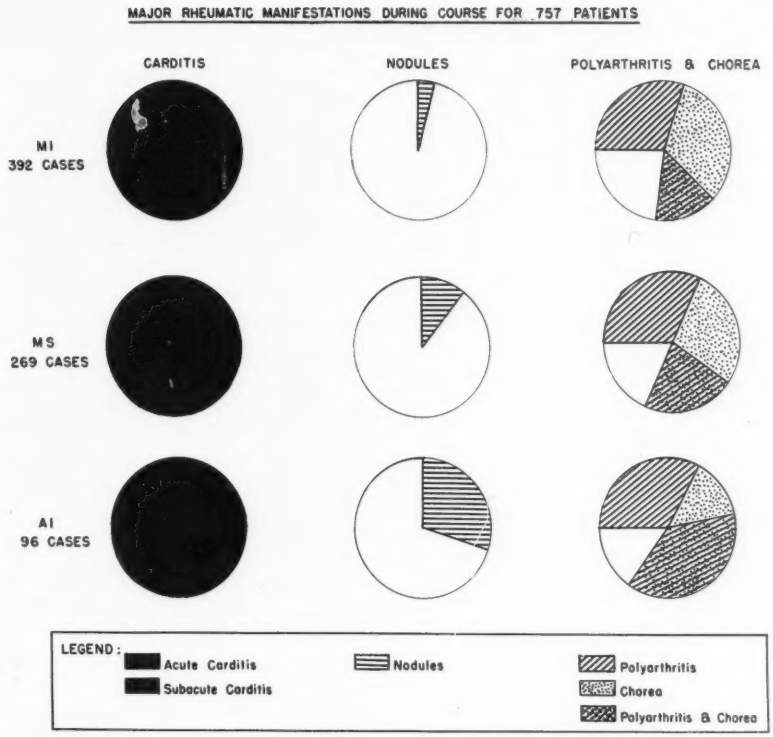

FIG. 1. Comparison of the relative incidence of the major manifestations of rheumatic fever experienced by 757 patients during the course of the disease, according to cardiac diagnosis at last observation.

with mitral insufficiency, acute carditis occurred in one or more attacks with or without subacute carditis in 14 per cent, and subacute carditis in 86 per cent. Only 1 patient experienced a recurrent attack of carditis during adult life. Subcutaneous nodules were observed in 3 per cent. Polyarthritis or chorea, or both, occurred one or more times in about three fourths of the patients; in one fifth, only minor manifestations were associated with the carditis.

There were 269 patients with physical signs of mitral stenosis and insufficiency. The clinical course was characterized in slightly less than one half of the patients by one or more attacks of acute carditis in addition to the frequent occurrence of subacute carditis. In slightly more than one half, the attacks of carditis were subacute. Subcutaneous nodules were observed in 9 per cent of these patients. Polyarthritis occurred in one or more attacks in about one third, and chorea in slightly less than one third. Polyarthritis and chorea occurred in about one fifth of the patients. In only 18 per cent was carditis associated with only minor manifestations. It is of some interest that the incidence of chorea in this group was not significantly different from that observed in the group with mitral insufficiency. After the age of 20 years, recurrent active carditis was observed clinically or pathologically in 7 patients.

Of the 96 patients who had combined aortic and mitral lesions, one or more attacks of acute carditis with or without subacute carditis was experienced by about three fourths; in only one fourth was the course characterized by one or more attacks of subacute carditis. Subcutaneous nodules occurred in 30 per cent. One or more attacks of polyarthritis occurred in about

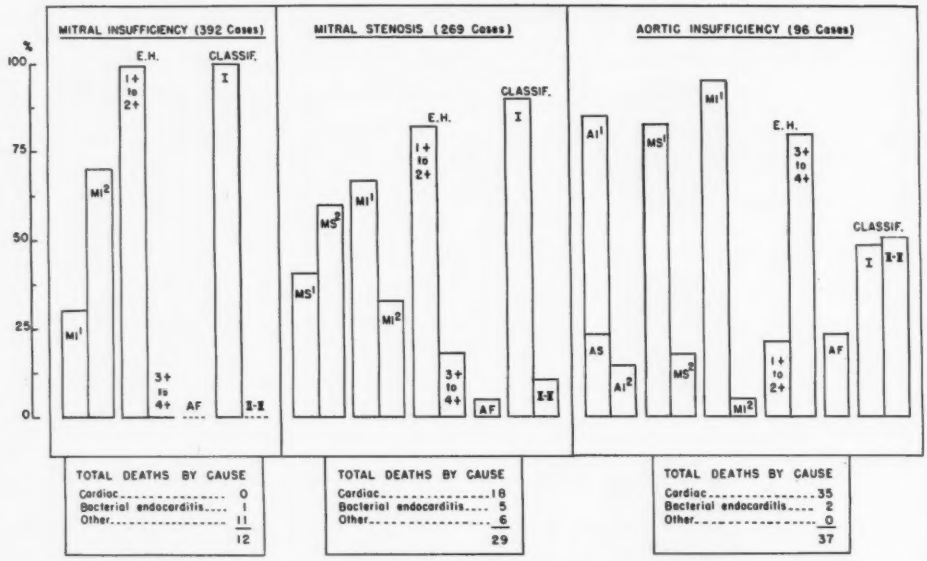

FIG. 2. Distribution of patients according to diagnosis at last observation. The valvular diagnosis was not changed when there was regression of auscultatory murmurs. [1], murmur constant; [2], murmur regressed; *EH 1–2+*, moderate cardiac chamber enlargement; *EH 3–4+*, marked cardiac chamber enlargement.

one third, and chorea in about one sixth; polyarthritis and chorea occurred in slightly less than one half. In about one tenth the associated manifestations were minor. Active carditis was demonstrated clinically or pathologically after the twentieth year in 13 patients.

In figure 2 there is presented a graphic description of the complete cardiac diagnosis at the last observation. The precordial systolic murmur remained constant and characteristic in about one third of the 392 patients with mitral insufficiency (MI^1); in two thirds it regressed over the years (MI^2). Before the age of 20, the murmur was constant and characteristic in about 50 per cent of the patients for 2 to 5 years, and in the remainder for 6 to 20 years. Of the murmurs that regressed, regression occurred after the age of 20 in 21 per cent, persisting in two thirds for 2 to 5 years and in one third for 6 to 20 years. Whether the murmur remained constant or regressed, cardiac chamber enlargement did not change. All but 1 patient had "moderate" cardiac chamber enlargement. It should be emphasized that increase in cardiac chamber enlargement with advancing age, or the appearance of new murmurs, was rarely noted. At last observation all of these patients were considered to be class I according to the New York Heart Association classification.[9] One hundred sixteen patients had experienced 1 to 5 pregnancies, and 113 men served in the Armed Forces. Of 12 deaths, 11 were due to noncardiac causes, and 1 to bacterial endocarditis.

Of the 269 patients with mitral stenosis, the diagnosis had been established in 79 per cent within 1 to 2 years of an observed attack of active carditis. The ages at which the diagnosis was recorded in one fifth of the patients ranged from 5 to 10 years, in less than one half between 10 to 15 years, and in about one fourth, from 15 to 20 years of age. The murmur of mitral stenosis was constant and characteristic in over one third (MS^1), remaining constant for a period of 5 to 30 years or more. In less than two thirds of the patients the murmur regressed (MS^2) after being constant and characteristic for a period of 2 to 5 years in one third, and 6 to 20 years or more in two thirds. The murmur of mitral insufficiency was con-

sant in about two thirds of these patients, and regressed in about one third. The regression of murmurs probably accounts for the reported incidence of isolated aortic insufficiency, and presumably for "pure mitral stenosis." In the majority of these patients there was cardiac chamber enlargement of "moderate" degree and in only one fifth was there "marked" enlargement. In the absence of recurrent carditis, cardiac chamber enlargement did not increase or change with age, whether auscultatory murmurs were constant or inconstant. Atrial fibrillation of 1 to 20 years' duration was present in 5 per cent. At last observation, in only 11 per cent was the functional classification II to IV. One hundred twelve patients had experienced 1 to 5 pregnancies, and 31 men served in the Armed Forces. Systemic emboli occurred in 4 patients. Of 29 deaths, 18 were due to cardiac causes, and 5 to bacterial endocarditis. Four of these patients died from 1 to 5 years following mitral valvulotomy.

Of the 96 patients with aortic lesions, the murmur of aortic insufficiency was constant in the majority, and in 14 (15 per cent) of the patients there was regression within 1 to 15 years. Twenty three patients also had aortic stenosis; in 2 there was tricuspid insufficiency. The murmur of mitral insufficiency was constant in 95 per cent; the murmur of mitral stenosis, in three fourths. Cardiac chamber enlargement was "marked" in three fourths of the patients. Atrial fibrillation was present in 24 per cent for a duration of 3 to 27 years. At last observation one half of this group was considered class II to IV. Fourteen patients experienced 1 to 3 pregnancies, and 6 men served in the Armed Forces. Five patients experienced systemic emboli. There were 37 deaths, 35 of which were attributed to cardiac causes. Active carditis occurred in 9, bacterial endocarditis in 2.

Comment

In this representative group of rheumatic children who reached the age of 20 years, about one half had a minimal degree of cardiac damage. In practically all of the patients the anatomic diagnosis was established by the age of 20 years. Furthermore, less than 3 per cent experienced a recurrent attack of carditis after the age of 20.

The frequency of the observed regression of systolic and diastolic murmurs during the clinical course needs emphasis. That absence of murmurs does not exclude persistence of valvular pathology has been demonstrated at postmortem and more recently during surgical exploration. The degree of residual cardiac damage and the constancy of murmurs paralleled the incidence of acute carditis. It is noteworthy that there was no significant difference in the incidence of attacks of polyarthritis or chorea in patients with mitral insufficiency or mitral stenosis. New murmurs or increasing cardiac chamber enlargement was rarely observed in the absence of rheumatic activity. Cardiac chamber enlargement did not appear to increase with time.

In 9 of the 53 patients whose death was attributed to cardiac causes, active carditis was demonstrated clinically or pathologically. The majority of the 8 deaths due to bacterial endocarditis occurred before the era of antibiotic therapy. Six patients who developed bacterial endocarditis during the past 6 years and were treated, are alive and asymptomatic. A more critical analysis of the morbidity of the majority of these patients, as well as consideration of factors contributing to the terminal event, will be presented in a subsequent report.[16]

Prognosis in Terms of Survivorship

Survivorship Subsequent to the Age of 20 (all cases)

The average annual mortality rate and probability of survival for 757 patients with rheumatic heart disease is presented in 5-year age groups in table 4, together with figures derived from the general United States population for the years 1939 to 1941,[14] which were corrected for sex ratio in our series. The over-all average annual mortality rate, based on a total of 9,347.5 person-years, is 8.3 per 1,000 (column 7). This may be compared with an average annual death rate of 3.1 per 1,000 in the United States general population as calculated for the same age distribution. The average annual

TABLE 4.—*Risk of Death at Five-Year Intervals, All Cases*

Age X to X + N	No. under observation at X years of age	No. living whose latest observation was X to X + N		Deaths between X and X + N	Person-years of observation between X and X + N	Average annual death rate per 1000	Probability of death in passing from X to X + 5 5qX	Probability of surviving from X to X + 5 5pX	Percentage surviving from age 20 to X	Percentage of U.S.A. population surviving from age 20 to X (1939–1941)	Age X
		Remaining	Lost								
20–25	757	54	26	28	3519.0	7.9	0.039	0.961	100	100	20
25–30	649	137	33	17	2801.5	6.0	0.030	0.970	96	99	25
30–35	462	192	9	16	1736.5	9.2	0.044	0.956	93	98	30
35–40	245	119	3	13	859.5	15.2	0.071	0.929	89	97	35
40–52	110	104	2	4	431.0	9.3	0.013	0.987	83	95	40
Total...		606	73	78	9347.5	8.3			82	93	45

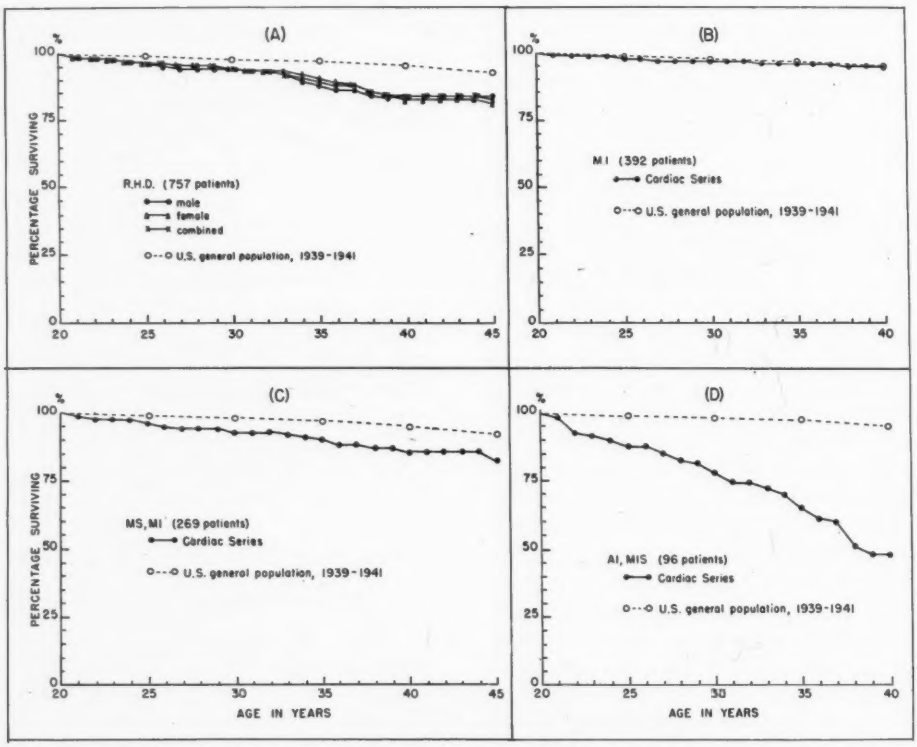

FIG. 3. Survivorship in cardiac series compared to that of the United States general population from 1939–1941. The horizontal scale gives the age, and the vertical scale the percentage estimated to survive to each age. *A*. All cases (757). *B*. 392 patients with mitral insufficiency. *C*. 269 patients with mitral stenosis and insufficiency. *D*. 96 patients with combined aortic and mitral lesions.

death rate appears to increase slightly with age as would be expected.

Survival to specific ages for patients reaching the age of 20 years (column 10) shows that 96 per cent survived to the age of 25, 93 per cent to the age of 30, 89 per cent to 35, and 82 per cent to the age of 45 years. Figure 3*A* shows graphically the percentage surviving to specific ages for the total group and for each sex. The horizontal scale gives the age, and the vertical

scale the percentage estimated to survive to each age. For comparison there is presented the survivorship for the general population of the United States from 1939 to 1941. There is no evidence of a sex difference in survivorship. Both the cardiac series and the general population show a gradual downward trend with advancing age but at about 33 years of age there is a sharper decline in survivorship in the cardiac series. Of those surviving to the age of 20, 82 per cent of the cardiac group survive to age 45, compared to 93 per cent for the general population.

Survivorship in Relation to Anatomic Diagnosis

To compare prognosis in terms of the type of valvular lesion and degree of cardiac chamber enlargement, life tables were constructed for each group (table 5). The over-all average annual mortality rate, over the ages 20 to 52, for 392 patients with mitral insufficiency was found to be 2.76 per 1,000 based on a total of 4,349 person-years. It is important to recall that the majority of deaths in this group were due to noncardiac causes. The death rate is not significantly different from that of the United States death rates previously quoted. Figure 3*B* shows that the survival curve for these patients is significantly better than that which obtained for patients with mitral stenosis and insufficiency (fig. 3*C*), and for combined aortic and mitral lesions (fig. 3*D*). In the group with mitral insufficiency the survival was 97 per cent at the age of 30, 96 per cent at 35, and 95 per cent at 40 years, which is essentially the same as that of the general population of the United States.[14]

For 269 patients with mitral stenosis and insufficiency the over-all average annual mortality rate is found to be 7.8 per 1,000, based on a total of 3,725.5 person-years, and is nearly 3 times greater than for mitral insufficiency alone. Comparison of the survivorship at specific ages revealed that 93 per cent survived to the age of 30 years, 90 per cent to 35, and 86 per cent to the age of 40 years. The survival curve for these patients shows a decline after about the age of 33, which is greater than for patients with mitral insufficiency alone but significantly less than for patients with combined aortic and mitral lesions (fig. 3*B–D*).

TABLE 5.—*Over-all Average Annual Mortality Rate by Valvular Lesion and Cardiac Size for 757 Patients 20 to 52 Years of Age*

Valvular lesion and cardiac size	Total cases	Total deaths	Total person-years of observation	Average over-all annual death rate/1,000
Mitral insufficiency				
with moderate EH..	*392**	*12*	*4349.0*	*2.76*
Mitral stenosis.....	*269*	*29*	*3725.5*	*7.78*
with moderate EH..	221	13	3170.0	4.10
with marked EH....	48	16	555.5	28.80
Aortic insufficiency...	*96*	*37*	*1273.0*	*29.0*
with moderate EH..	20	2	263.0	7.60
with marked EH....	76	35	1010.0	34.60
Cardiac Size				
moderate EH (1–2+)	632	27	7735.5	3.49
marked EH (3–4+)..	125	51	1612.0	31.60

EH = enlargement of heart.
* includes one case of marked EH.

For the 96 patients with combined aortic and mitral lesions the over-all average annual mortality rate is 29 per 1,000, based on a total of 1,273 person-years. Figure 3*D* indicates that the survival curve drops precipitously after 30 years of age; 78 per cent of these patients survived to age 30, 65 per cent to 35, and 49 per cent to the age of 40 years.

A comparison of mortality according to heart size (table 5) reveals an over-all average annual mortality rate of 3.5 per 1,000 for a total of 7,736 person-years for 632 patients having moderate enlargement of the heart, compared to 31.6 per 1,000 for a total of 1,612 person-years in 125 patients with marked enlargement. Survival rates are significantly lower for patients with marked cardiac enlargement than for those with moderate enlargement, as shown in figure 4*A*. In the group with moderate enlargement of the heart, 97 per cent survived to the age of 30 compared to 78 per cent for patients with marked enlargement, and 93 per cent still survived at 40 years compared to 48 per cent for those with marked enlargement.

Further comparison of mortality in patients with mitral stenosis according to degree of cardiac enlargement (table 5) shows an over-all

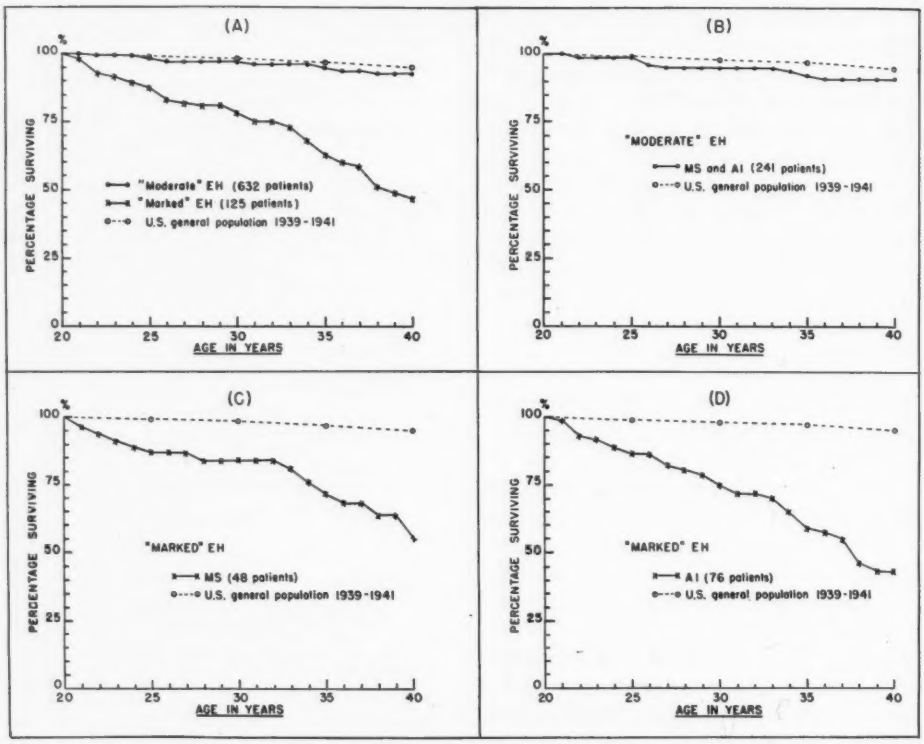

FIG. 4. Comparison of survivorship according to heart size and valvular lesion for: *A*. "Moderate" and "marked" cardiac chamber enlargement. *B*. "Moderate" cardiac enlargement with mitral stenosis and insufficiency, or combined mitral and aortic lesions. *C*. "Marked" cardiac enlargement with mitral stenosis and insufficiency. *D*. "Marked" cardiac enlargement with combined mitral and aortic lesions.

average annual mortality rate of 4.1 per 1,000 for moderate enlargement compared to 28.8 per 1,000 for patients with marked cardiac enlargement.

For patients with combined aortic lesions and moderate enlargement of the heart, the over-all average annual mortality rate was 7.6 per 1,000 compared to 34.6 for patients with marked enlargement.

Although the total person-years of observation for some of the subgroups is rather small, the consistency of the comparisons and the trend in survival curves appear to indicate that degree of cardiac enlargement is an important factor in influencing survivorship (fig. 4*B*, C, *D*). It is of interest that insurance mortality investigations of physical impairment also concluded that the degree of cardiac enlargement affected survivorship adversely.[15]

Comment

Interpretation of the data presented on mortality and survivorship for patients with rheumatic heart disease must take into account the representativeness of the sample subject to analysis.

Unlike the previous study on longevity in rheumatic fever[1] where children were included at onset of the disease at various ages, this analysis concerns only those children who reached the age of 20 years. All the patients were kept under continuous medical supervision as part of a long-term study of the natural history of rheumatic heart disease. As stated earlier, they are not comparable to a series of

patients seeking medical attention because of cardiopulmonary symptoms, and any estimate of mortality risk based on such a symptomatic group would greatly exaggerate the true mortality for persons having a history of rheumatic fever.

When the results of this study are compared with those of the previous one,[1] it is seen that the over-all average mortality rate in the third, fourth, and fifth decades is 8.3 per 1,000 per year, about half that obtained during the first 2 decades of life (16.0 per 1,000 per year).

It is significant that for the 391 patients with mitral insufficiency and moderate cardiac enlargement the survival curve, after 20 years of age, followed closely that of the general population.

The importance of degree of cardiac chamber enlargement is indicated by the low survival rates among patients with marked cardiac enlargement. The morbidity experienced by a majority of these patients will be considered in a subsequent study.[16]

Discussion

Prognosis for patients with rheumatic heart disease who reached the age of 20 years is obviously dependent on the degree of residual cardiac damage sustained during the earlier years. It is significant that in about 50 per cent of the patients, residual cardiac damage was characterized by mitral insufficiency and moderate cardiac enlargement. In two thirds of these patients the auscultatory murmurs regressed and cardiac chamber enlargement would not have been recognized on physical examination or by the usual radiographic examination limited to the posteroanterior view. These patients are probably representative of those individuals who have had rheumatic fever and are considered to be without clinical evidence of heart disease. It is important to note that when patients in this study were noted to have regression of characteristic murmurs with persistent cardiac chamber enlargement, the valvular diagnosis was not changed. It is probable that patients who are considered to have "pure" mitral stenosis or isolated aortic insufficiency may have had regression of the characteristic murmurs of mitral lesions.

The significance of the relation of the extent of residual cardiac damage to the severity of carditis is illustrated by the relative increased incidence of acute carditis among patients with mitral stenosis and combined aortic lesions and markedly enlarged hearts. It is perhaps of some significance that among these patients, so-called "delayed" appearance of mitral stenosis was rarely observed in the absence of clinical evidence of rheumatic carditis. The diagnosis of mitral stenosis was recorded in the majority of patients within 1 to 2 years of an observed attack of carditis.

In practically all of the patients the anatomic diagnosis was established by the age of 20 years. It is apparent therefore that it is during childhood that cardiac damage must be prevented. Our recent observations,[17] demonstrating that early adequate short-term hormone therapy in active carditis will result in diminished residual cardiac damage, offer justification for the prediction that the survival rate for patients so treated, reaching the age of 20, will approximate that which is observed for the 50 per cent of patients with minimal cardiac damage.

At the present time it is not possible, from published data, to assess the effect of surgical intervention on longevity. However, if it were found that survival rates were favorably affected, particularly among patients with marked cardiac enlargement and combined valvular lesions, earlier surgical intervention may be indicated as suggested by many surgeons. Whether an even more favorable survivorship would result for patients with valvular lesions and moderate cardiac enlargement following surgical intervention must await controlled studies.

It must again be emphasized that the survival rates for patients with rheumatic heart disease as presented refers to a series of patients with rheumatic heart disease who were kept under supervision from childhood. Of significance is the fact that for those who had mitral insufficiency with moderate cardiac enlargement, comprising about one half of the

total group, the survival rate followed closely that of the general population. In a series of adult patients who seek medical attention because of cardiopulmonary symptoms, survivorship would not be expected to be as favorable.

Summary

The observed natural history of rheumatic heart disease is presented for the 757 out of 1,042 rheumatic children who reached the age of 20 years and have been followed subsequently to various ages up to 52 years. During the 40-year period of observation, of the 757 patients who reached 20 years of age, about three fifths have been followed beyond 30 years of age, one third beyond 35 years, and one seventh beyond 40.

During the clinical course, acute carditis with or without subacute carditis occurred in one or more attacks in one third, and subacute carditis in two thirds. Of the associated major manifestations polyarthritis occurred in one or more attacks in one third, chorea in another third, and polyarthritis and chorea in about one sixth of the patients. Carditis was associated with only minor manifestations in about one fifth.

The degree of residual cardiac damage and the constancy of murmurs was found to be closely related to the relative incidence of acute carditis during childhood. Increasing cardiac involvement in the absence of recurrent carditis was not noted with the passage of time. Recurrent carditis occurred in less than 3 per cent of the patients after the age of 20 years.

The anatomic diagnosis was established by the age of 20 years in practically all of the patients. In four fifths, cardiac chamber enlargement was "moderate" and in one fifth it was "marked." In more than one half of the patients there was mitral insufficiency, in one third mitral stenosis and insufficiency, and in one eighth there were combined aortic and mitral lesions. The diagnosis of mitral stenosis was established in 79 per cent within 1 to 2 years of an observed attack.

Of the 78 deaths, 68 per cent were due to cardiac causes, 10 per cent to bacterial endocarditis, and 22 per cent to noncardiac causes. The over-all average mortality rate was 8.3 per 1,000 per year for patients 20 to 52 years of age compared to 16 per 1,000 per year for those under 20. The comparable United States mortality rate for 1940, for the ages 20 to 52 years (adjusted to the cardiac age distribution) was 3.1 per 1,000 per year. The average annual mortality rate for 392 patients with mitral insufficiency was 2.8 per 1,000; for 269 patients with mitral stenosis and insufficiency, 7.8 per 1,000; and for 96 patients with combined mitral and aortic lesions, 29 per 1,000.

The survival curve for the entire group of patients who reached the age of 20 showed that an estimated 82 per cent of them would reach the age of 45 as compared with 95 per cent in the general population. There was no evidence of a sex difference in survivorship. The survival curve for patients with mitral insufficiency followed closely that of the general population, while for patients with mitral stenosis and insufficiency there was a decline after about 33 years of age, which is greater than for mitral insufficiency alone but less than for combined aortic and mitral lesions. Only about one half of this latter group who reached the age of 20 survived to the age of 40.

The over-all average mortality rate for moderate enlargement was 3.5 per 1,000 compared to 31 per 1,000 for marked enlargement. The survival curves according to degree of heart enlargement are markedly different. Of the persons who survived to the age of 20, 93 per cent survived to the age of 40 when the heart enlargement was "moderate" while only 40 per cent survived to 40 when the heart enlargement at age 20 was "marked." When valvular lesions and heart enlargement are considered simultaneously, heart size appears to be the more important factor in relation to survivorship.

Acknowledgment

We gratefully acknowledge our indebtedness for constructive criticisms and suggestions to Margaret Merrell, Sc.D. of The Johns Hopkins University, Baltimore, Md., and to Irwin D. J. Bross, Ph.D., of the Cornell University Medical College, New York, N. Y.

Summario in Interlingua

Es presentate le observate historia natural de rheumatic morbo cardiac in 757 ex 1,042 juveniles rheumatic, qui attingeva le etate de 20 annos e esseva observate subsequentemente usque a varie etates infra le maximo de 52 annos. In le curso del periodo de 40 annos de observation, circa tres quintos del 757 patientes passante le etate de 20 annos esseva observate usque a ultra le etate de 30 annos, un tertio usque a ultra le etate de 35 annos, e un septimo usque a ultra le etate de 40 annos.

Durante le curso clinic del morbo, carditis acute con o sin carditis subacute occurreva in un o plure attaccos in un tertio del patientes; carditis subacute in duo tertios. Quanto al associate manifestationes major, polyarthritis occurreva in un o plure attaccos in un tertio del patientes; chorea in un altere tertio; e polyarthritis e chorea insimul in circa un sexto. Carditis esseva associate solmente con manifestationes minor, con un incidentia de circa un quinto.

Esseva trovate que le grado de residue lesiones cardiac e le constantia de murmures esseva nettemente relationate al incidentia relative de carditis acute durante le etate juvenil del patientes. Un augmento del affectiones cardiac in le absentia de recurrente carditis esseva notate con le passage de tempore. Recurrente carditis occurreva in minus que 3 pro cento del patientes post le etate de 20 annos.

Le diagnose anatomic esseva establite ante le etate de 20 annos in practicamente omne casos. In quatro quintos, le allargamento del cameras cardiac esseva "moderate," e in un quinto illo esseva "marcate." Insufficientia mitral esseva presente in plus que un medietate del patientes; stenosis mitral con insufficientia in un tertio; e combinate lesiones aortic e mitral in un octavo. Le diagnose de stenosis mitral esseva establite in 79 pro cento del casos intra 1 a 2 annos post le observation de un attacco.

Inter le 78 mortes, 68 pro cento resultava de causas cardiac, 10 pro cento de endocarditis bacterial, e 22 pro cento de causas noncardiac. Le magnitude medie del mortalitate general esseva 8,3 pro mille per anno pro patientes de inter 20 e 52 annos de etate e 16 pro mille per anno pro patientes infra 20 annos de etate. Le comparabile mortalitate in le Statos Unite pro le anno 1940 (corrigite secundo le distribution de etates in le gruppo cardiac) esseva 3,1 pro mille per anno pro individuos de inter 20 e 52 annos de etate. Le magnitude medie del mortalitate annual inter le 392 patientes con insufficientia mitral esseva 2,8 pro mille; inter le 269 patientes con stenosis e insufficientia mitral 7,8 pro mille; e inter le 96 patientes con combinate lesiones mitral e aortic 29 pro mille.

Le curva de superviventia pro le gruppo total de patientes passante le etate de 20 annos monstrava que un estimate proportion de 82 pro cento de illes attingerea le etate de 45 annos, in comparation con 95 pro cento in le population general. Le superviventia manifestava nulle evidente differentias secundo le sexo del patientes. Le curva de superviventia pro patientes con insufficientia mitral sequeva strictemente le correspondente curva pro le population general, durante que le curvas pro le altere sub-gruppos monstrava que in patientes con stenosis e insufficientia mitral il occurre post le etate de circa 33 annos un declino que es plus marcate que in le caso de patientes con insufficientia mitral sol sed minus marcate que pro patientes con combinate lesiones aortic e mitral. In iste ultime gruppo, non plus que circa un medietate del individuos passante le etate de 20 annos superviveva usque al etate de 40 annos.

Le magnitude medie del mortalitate general in casos de moderate allargamento cardiac esseva 3,5 pro mille. In casos de marcate allargamento illo esseva 31 pro mille. Le curvas de superviventia secundo le grado del allargamento cardiac esseva multo differente. Inter le individuos qui passava le etate de 20 annos, 93 pro cento superviveva usque al etate de 40 annos si lor allargamento cardiac esseva "moderate." Solmente 40 pro cento de illes superviveva usque a ille etate si lor allargamento cardiac al etate de 20 annos esseva "marcate." Quando on considera le lesiones valvular juxta le allargamento cardiac, il pare

que le dimensiones cardiac representa un factor plus importante ab le puncto de vista del superviventia.

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The Foxglove when given in very large and quickly-repeated doses, occasions sickness, vomiting, purging, giddiness, confused vision, objects appearing green or yellow; increased secretion of urine with frequent motions to part with it, and sometimes inability to retain it; slow pulse, even as slow as 35 in a minute, cold sweats, convulsions, syncope, death.—William Withering. *An Account of the Foxglove, and Some of Its Medical Uses.* Birmingham, 1785.

The Natural History of Rheumatic Heart Disease in the Third, Fourth, and Fifth Decades of Life

II. Prognosis with Special Reference to Morbidity

By Melville G. Magida, M.D., and Franklin H. Streitfeld, M.D

This report is intended to contribute to an understanding of the natural morbidity of patients with chronic rheumatic heart disease in the third, fourth, and fifth decades of life. The data should prove useful in a consideration of the criteria for surgical intervention.

THE recent emphasis on early surgical intervention for patients with chronic rheumatic valvular disease has made the need for basic data concerning the natural history of this condition of practical importance.

Data regarding the natural morbidity of patients with chronic rheumatic heart disease in the third, fourth, and fifth decades of life are presented. This information should prove useful in evaluating the effects of surgical intervention on the natural morbidity and mortality of the disease.[1-3]

Methods and Materials

Of 757 adult patients with rheumatic heart disease analyzed in the previous study on survivorship,[1] 385 patients were examined and followed by the authors personally during 1953 to 1955. All of these patients have been under medical supervision in the same cardiac clinic since childhood as part of a long-term follow-up study. They were therefore not comparable with a group of adults attending a cardiac clinic because of cardiopulmonary symptoms.

There were 160 males and 225 females, and this sex ratio held true for the subgroups studied. All patients were examined an average of 6 times in the 3-year period. Patients with cardiopulmonary symptoms were seen more frequently. On each visit they were questioned concerning their tolerance to physical stress in home, employment, leisure, and sport activities. Physical examination was amplified by fluoroscopic examination, electrocardiogram, and determination of vital capacity. Fluoroscopic examination included 3 standard positions and the use of barium.

In addition, the records of 78 patients who were under observation during the 40-year period and who died after the age of 20 were included for analysis of the morbidity experienced prior to death and the postmortem findings in 25 patients. The diagnosis of the type of valvular deformity was made according to the criteria of the New York Heart Association.[4] The anatomic diagnosis was established in the majority of patients by the twentieth year. The persistence of murmurs and their regression for 2 or more years were noted. There were 173 patients with mitral insufficiency alone, and 161 with mitral insufficiency and stenosis of whom 1 also had tricuspid insufficiency; 51 patients had combined mitral and aortic valvular disease including 11 with aortic stenosis and 1 with tricuspid insufficiency.

Cardiac enlargement was classified as minimal, moderate, or marked, fluoroscopically. Heart size was determined according to the shape of the cardiac silhouette in the posteroanterior projection, the angle of clearance of the left ventricle in the left anterior oblique projection, prominence of the pulmonary artery segment and atrial displacement of the barium-filled esophagus in the right anterior oblique projection (graded 1+, 2+, 3+), and enlargement of the right ventricle in the oblique projection.

Minimally enlarged hearts included those with a normal cardiac silhouette in the posteroanterior projection, an angle of clearance of the left ventricle of 55 degrees, and 1+ retrodisplacement of the esophagus in the right anterior oblique projection. Moderately enlarged hearts included those with minimal or moderate increase in the cardiac silhouette in the posteroanterior projection, an angle of clearance of 60 degrees or 60+ degrees, 2+ retrodisplacement of the esophagus in the right anterior oblique projection, and slight right ventricular enlargement. Markedly enlarged hearts included all those in which the dimensions exceeded the above in all projections.

Twelve-lead electrocardiograms were recorded with standard, unipolar extremity, and precordial leads.

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Vital capacities were measured with a water displacement, cylindrical spirometer. Each patient's prior maximum reading served as the basis for comparison with subsequent recordings. Acute respiratory infections excluded, the normal range referred to 90 per cent or more of the previous maximum. Moderate reduction is defined as 75 to 89 per cent of maximum. Less than 75 per cent is defined as marked reduction.

For purposes of analysis all the patients were grouped arbitrarily on the basis of their cardiopulmonary symptoms. This modified functional cardiac classification corresponds with that most commonly used[5] in the selection of such patients for valvular surgery. Functional class I, including 340 patients, consists of those patients with no or minimal symptoms of cardiopulmonary disability. Class II, including 20 patients, contains those patients who had symptoms and disability of but moderate degree that were not progressive in nature. Class III, including 13 patients, contains those who were clearly and progressively ill with advancing symptoms of cardiopulmonary disability. Class IV, including 12 patients, contains those with extreme disability.

Observations

Mitral Insufficiency

There were 173 patients with mitral insufficiency, of whom 85 were in the third decade of life, 78 in the fourth, and 10 in the fifth (table 1). In over 70 per cent there was regression of a previously long-standing apical systolic murmur. Patients with persistent murmurs had a higher incidence of moderately enlarged hearts. Sixty per cent of the patients had minimal cardiac enlargement, and the remainder had moderate enlargement. None had very large atrial chambers or detectable right ventricular hypertrophy. Progressive cardiac chamber enlargement was not noted with advancing age. Active carditis was not observed in any patient after age 20. These patients were asymptomatic or had minimal complaints of dubious significance. They were apparently unimpaired functionally and leading normal, active lives. Pregnancies were well tolerated as were other intercurrent stresses and illnesses. Ten per cent of the patients had significantly reduced vital capacities not correlating with the persistence or regression of murmurs, or the degree of cardiac enlargement; these few patients presumably were not aware that their reactions to exertion were not normal. All 173 patients, included in functional class I, would not be considered to warrant surgical intervention (table 2, fig. 1).

Table 1.—*Diagnostic Classification for 385 Patients According to Decades*

Decade	MI	MI, MS	MI, MS and aortic valvular disease	Totals
Third	85	52	20	157
Fourth	78	79	19	176
Fifth	10	30*	12*	52
Total	173	161	51	385

* Including 1 patient with tricuspid insufficiency.

Mitral Stenosis and Insufficiency

There were 161 patients with mitral stenosis and insufficiency; 52 were in the third decade of life, 79 in the fourth, and 30 in the fifth (table 1). One hundred thirty-four patients were included in functional classification I, 13 in class II, 10 in class III, and 4 patients in class IV (table 2, fig. 1).

Functional Classification I. One hundred thirty-four patients had no or minimal cardiopulmonary symptoms; 47 were in the third decade of life, 67 in the fourth, and 20 in the fifth. In 36 patients the diastolic and systolic murmur persisted, in 44 both murmurs regressed, and in 54 only the diastolic murmur regressed. There were no instances of so-called "pure" mitral stenosis in this group. It will be recalled that the valvular diagnosis was not changed when murmurs regressed. After the age of 20 years, 4 patients experienced active carditis, including 1 patient with 3 episodes. Cardiac enlargement was minimal in 39 per cent, moderate in 55 per cent, and marked in 6 per cent. There were only 8 patients in whom right ventricular enlargement was detected fluoroscopically. No significant progression in cardiac chamber enlargement was observed with advancing age. Multiple electrocardiograms of 117 patients were available. Normal records were noted in 76 patients (65 per cent), broad notched P waves in 24 per cent, evidence of left ventricular hypertrophy in 9 per cent, and right ventricular hypertrophy in only 2 patients.

TABLE 2.—*Distribution According to Cardiopulmonary Symptoms*

Functional classification	Decade	MI heart enlargement			MI, MS heart enlargement			AI, MIS, MS* heart enlargement			Total
		min.	mod.	mkd.	min.	mod.	mkd.	min.	mod.	mkd.	
I	Third	47	37	1	19	25	3	0	8	9	
	Fourth	44	34	0	21	42	4	0	9	2	
	Fifth	7	3	0	12	7	1	0	3	2	
	Total.....	98	74	1	52	74	8	0	20	13	340
II	Third				0	2	2	0	0	1	
	Fourth				1	2	2	0	1	1	
	Fifth				0	3	1	0	1	3	
	Total.....				1	7	5	0	2	5	20
III	Third				0	0	1	0	0	0	
	Fourth				0	0	4	0	0	3	
	Fifth				0	1	4	0	0	0	
	Total.....				0	1	9	0	0	3	13
IV	Third				0	0	1	0	0	2*	
	Fourth				1	0	1*	0	0	3	
	Fifth				0	0	1	0	2	1	
	Total.....				1	0	3	0	2	6	12

* Eleven of these patients also had aortic stenosis.
† These patients also had tricuspid insufficiency.

Vital capacity was within normal limits in 75 per cent of this group; 19 per cent had moderate, and 6 per cent marked reduction. Nearly all of the patients in the third decade, but only about half those in the fifth decade, had normal vital capacities. Marked reduction was limited to the fourth and fifth decades. Vital capacity did not correlate with heart size or with the persistence or regression of the murmurs, and it is likely that the reduction in vital capacity in the older asymptomatic patient may be related, at least in part, to loss of pulmonary elasticity secondary to aging. As in the mitral insufficiency group, they apparently were unaware of any abnormal reaction to effort. Fifty-five of the 88 women in this group had been pregnant. The total number of pregnancies was 130. Among these asymptomatic patients, pregnancy did not appear to influence adversely the cardiopulmonary status. This group, at the present time, would probably not be considered candidates for surgical consideration.

Functional Classification II. Thirteen patients are included in functional classification II because of persistent but nonprogressive cardiopulmonary symptoms of mild to moderate degree. The murmurs were persistent in all. There were 4 patients in the third decade of life, 5 in the fourth, and 4 in the fifth. All but 1 of the patients had moderately or markedly enlarged hearts that did not appear to increase with advancing age. Six had fluoroscopic evidence of right ventricular enlargement; all had left atrial and left ventricular enlargement. Electrocardiograms were normal in 5 patients. Changes indicative of right ventricular hypertrophy were noted in 3 patients, of left in 4, and 8 patients had abnormal atrial complexes.

Vital capacity was within normal limits in 7 patients although these had subjective complaints. It was moderately reduced in 5, and markedly in 1. After the age of 20, 1 patient experienced an attack of active carditis, and 4 developed atrial fibrillation. Of the 11 women in this group, 9 had a history of 20 pregnancies. All but 3 patients tolerated their pregnancies

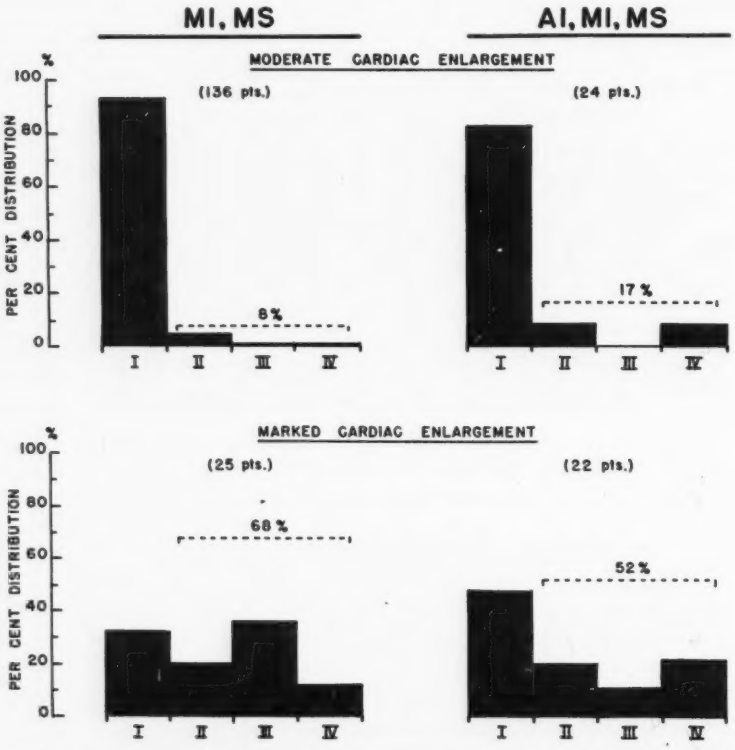

FIG. 1. Comparison of functional classification and extent of cardiac enlargement for 212 patients with mitral insufficiency and mitral stenosis and combined aortic lesions.

well. One woman developed congestive heart failure, and another developed chronic atrial fibrillation during the first pregnancy but withstood her second pregnancy well. In a third patient a mitral diastolic murmur that had temporarily regressed, reappeared with her second pregnancy and persisted. These 13 patients, according to most observers, would be considered probable candidates for surgery.

Functional Classification III. Ten patients had progressive cardiopulmonary symptoms. The majority were in the fourth and fifth decades of life. All had persistent murmurs. All but 1 had marked cardiac enlargement. Nearly every patient had electrocardiographic evidence of left ventricular and right ventricular hypertrophy, and atrial involvement. After the age of 20, 1 patient experienced active carditis. Five had atrial fibrillation. All patients had reduction in vital capacity, most of them marked. Four women experienced 10 pregnancies. One of these developed a concomitant subacute bacterial endocarditis and another 2 patients developed persistent hypertensive cardiovascular disease after pregnancy with a subsequent increase in cardiopulmonary symptoms. Several of these patients would be considered candidates by many surgeons.

Functional Classification IV. Four patients had extreme cardiopulmonary symptoms. There was 1 patient in the third decade of life, 2 in the fourth, and 1 in the fifth. Three patients had marked cardiac enlargement, marked reduction in vital capacity and intractable congestive heart failure; 1 of these had associated tricuspid insufficiency. The remaining patient had idiopathic pulmonary fibrosis and insufficiency. None had had active carditis after age 20; 2 patients developed atrial fibrillation. One patient had been pregnant 3 times. In all instances, electrocardiograms indicated ventricular hypertrophy and abnormal atrial com-

plexes. At the present time most of these patients would not be considered suitable for surgical intervention.

Combined Mitral Stenosis and Insufficiency, and Aortic Valvular Disease

Fifty-one patients with mitral stenosis and insufficiency had associated aortic valvular lesions. All had aortic insufficiency; 11 had aortic stenosis. One had tricuspid insufficiency. Twenty patients were in the third decade of life, 19 in the fourth, and 12 in the fifth (table 1). There were 33 patients in functional classification I, 7 in class II, 3 in class III, and 8 patients in class IV (table 2, fig. 1).

Functional Classification I. Thirty-three patients were asymptomatic; 17 in the third decade of life, 11 in the fourth, and 5 in the fifth. There were 4 instances of aortic stenosis. In 25 patients the murmurs were persistent. Among the other 8 patients, the murmur of mitral insufficiency subsequently regressed in 4, that of mitral stenosis in 5, and that of aortic insufficiency in 6 patients. In 4 patients the murmurs of mitral stenosis and aortic insufficiency both regressed, but not simultaneously. Only 14 patients had a characteristic widened pulse pressure. It is possible that in some patients the basal diastolic murmur may have represented pulmonary incompetency. Twenty patients had moderate and 13 had marked cardiac enlargement. All of the patients had fluoroscopic evidence of left atrial and left ventricular enlargement, and none had demonstrable right ventricular enlargement. In 32 patients multiple electrocardiograms were available. Seventeen patients had normal tracings. All the remaining 15 had the abnormal P waves usually associated with mitral stenosis, and 11 of them had evidence of left ventricular hypertrophy; none had right ventricular hypertrophy.

Three patients had had an acute attack of active carditis after the age of 20. Five of the 12 women in this group had been pregnant a total of 8 times without untoward effect. Only one third of the patients had more than minimal reduction of vital capacity, and only 1 had marked reduction. Few of these 33 patients, according to commonly accepted criteria, would be considered candidates for surgery at the present time.

Functional Classification II. There were 7 patients who had persistent but not progressive cardiopulmonary symptoms of mild or moderate degree. All but 1 of them were in the fourth and fifth decades of life. One patient had aortic stenosis. In 2 patients the murmur of aortic insufficiency had regressed. Three patients had wide pulse pressures. Two had moderate and 5 had marked cardiac enlargement fluoroscopically, with left atrial and left ventricular enlargement in all, and detectable right ventricular enlargement in 5. Electrocardiograms were available for each patient; only 1 tracing was a normal record. Three patients had abnormal atrial complexes and 4 had left ventricular hypertrophy. None showed evidence of right ventricular hypertrophy. Three episodes of active carditis were experienced by each of 2 patients after the age of 20. Four of the 5 women had been pregnant a total of 5 times without exaggeration of disability. Two patients had minimal, 4 moderate, and 1 marked reduction of vital capacity. Some of these patients might be considered suitable for cardiac surgery at the present time.

Functional Classification III. Three patients, all in the fourth decade, had progressive cardiopulmonary symptoms. One had aortic stenosis. The murmur of aortic insufficiency had regressed in 1 patient. None had a wide pulse pressure. All had marked cardiac enlargement fluoroscopically, including the left atrium and both ventricles. Electrocardiograms disclosed abnormal atrial complexes in each patient, with evidence of left ventricular hypertrophy in 2 and of right ventricular hypertrophy in none. One patient had had active carditis after age 20. All 3 patients had a moderately reduced vital capacity. All had been in congestive heart failure on one or more occasions, and 2 had chronic atrial fibrillation. These 3 patients might be considered likely candidates for cardiac surgery by some surgeons.

Functional Classification IV. Eight patients with mitral and aortic valvular disease had extreme symptoms of cardiopulmonary disability; 2 were in the third decade of life, and 3 in each of the fourth and fifth decades. Two of the older

patients had advanced portal cirrhosis and coronary arteriosclerosis respectively, with moderate cardiac enlargement. The remaining 6 patients had severe aortic valvular disease and marked over-all cardiac enlargement. Five of them had wide pulse pressures. Five had the murmur and thrill of aortic stenosis, and one of them had tricuspid insufficiency as well. Three of them were in chronic congestive heart failure, and 1 had atrial fibrillation.

Only the patient with portal cirrhosis had a normal electrocardiogram. The others had records showing left ventricular hypertrophy and abnormal P waves but not right ventricular hypertrophy. There were 2 instances of carditis after age 20. One woman experienced 2 pregnancies without complications. Nearly every patient had markedly reduced vital capacities. None of these 8 patients would be considered suitable for surgical intervention.

Additional Observations

Of the total 385 patients, only 45 had cardiopulmonary symptoms. There were 28 patients with mitral stenosis and insufficiency alone, and 17 with associated aortic disease. Possible factors that may have been responsible for the morbidity after age 20 were considered. All but 1 of these patients were in functional classification I for 2 to 24 years, averaging 10.5 years, and progressed variously to functional classification II, III, and IV. There were 71 instances of such a change among the 45 patients with single or multiple shifts in symptomatic status. Forty-one patients progressed from an asymptomatic state to functional classification II. Eighteen developed progressive symptoms and entered class III. Twelve eventually developed extreme cardiorespiratory symptoms and were included in functional classification IV.

In 60 instances of a change in symptomatic status, factors were identified that might have been causally related to the development of subjective complaints of dyspnea associated with the objective findings of decreased vital capacity, increased heart size, or congestive heart failure. Among these 60 instances of changed morbidity, decreasing vital capacity, further cardiac chamber enlargement, and congestive heart failure either as an episode or continuous and intractable, characterized the course. In 8 instances active carditis was responsible; in an additional 2 instances, active carditis may have occurred when these patients were not under our medical supervision. In 14 instances the onset of atrial fibrillation attended the changed symptomatic status. In 6 instances there was progressive deterioration from an asymptomatic state to functional classification IV, due to cirrhosis in one, chronic pulmonary disease in a second, and the development of hypertensive or arteriosclerotic heart disease in 4. In 22, other factors were identified with a change in functional classification. These included pneumonia in 15, healed subacute bacterial endocarditis in 3, and thromboembolism in 4. Whether there was an associated subacute carditis in some of these patients could not be ascertained. In 8 instances pregnancy was associated with a change in morbidity.

There were 11 instances of change in clinical status in which no causal factor could be identified to explain the change in functional classification. In 3, it represented a change from class I to class II; in 4, a change from class II to III, and in 4 a change from class II or III to class IV. All of these patients had marked cardiac enlargement with mitral stenosis and insufficiency and aortic stenosis and insufficiency that were present since age 20. It is possible that changes in symptomatic status were related to the progressive influence upon the circulation of chronic valvular disease. However, the extent of myocardial damage and the presence of unrecognized carditis must be considered.

Further information pertinent to the study of the natural morbidity of rheumatic heart disease was available from the records of 45 of 53 patients who died of cardiac causes after surviving to the age of 20 years or more.

There were 14 patients with mitral stenosis whose records were suitable for analysis; 7 were in the third decade of life, 4 in the fourth, and 3 in the fifth decade. Of those in the third decade, all were asymptomatic until within 1 year or less of death. Five had moderate cardiac enlargement. In 5, death was sudden, and in 2 of these pregnancy was a complicating feature. Two patients with marked cardiac enlargement became symptomatic with the onset of atrial

fibrillation. Of the 4 patients in the fourth decade of life, all had cardiopulmonary symptoms for a period of 2 to 7 years. All but 1 had marked cardiac enlargement. Two had had mitral valve surgery, one of whom survived 3 years but had no change in functional status, and the other remained in intractable congestive heart failure for the year following surgery. Of the 3 patients in the fifth decade of life, all had marked cardiac enlargement and atrial fibrillation with cardiopulmonary symptoms for 2 to 6 years before death. Two patients had had valvulotomy; one survived for 2 years without improvement, and the other succumbed after 4 years with pulmonary embolism.

There were 31 patients with aortic and mitral valve disease. Nine of these had demonstrable carditis as the terminal event; 4 of these were asymptomatic prior to their terminal event for a period of 2 to 9 years, 3 had atrial fibrillation, and 2 had severe intractable congestive heart failure for 3 and 5 years respectively before death. Of the remaining 22 patients who died, 9 were in the third decade of life, 12 in the fourth, and 1 in the fifth decade. In the third decade, all but 1 patient had marked cardiac enlargement, and 5 had atrial fibrillation. One patient sustained sudden death from pulmonary embolism, and 2 had a preceding subacute bacterial endocarditis. They had been asymptomatic for 1 to 9 years. In the fourth decade of life, all but 1 of the 12 patients had marked cardiac enlargement, and 10 had atrial fibrillation. The majority were asymptomatic for a period of 6 to 15 years. Five patients had a sudden death, presumably embolic in nature. The 1 patient in the fifth decade of life, with marked cardiac enlargement and atrial fibrillation, who had been asymptomatic for 19 years, had nonprogressive symptoms for an additional 4 years and then experienced pulmonary edema within 6 months of her terminal episode, which was associated with bronchopneumonia.

It is of interest that of the 45 patients whose death was attributed to cardiac causes, carditis, fibrillation, pulmonary embolism, and pneumonia were identified as common factors that appeared to induce the terminal event.

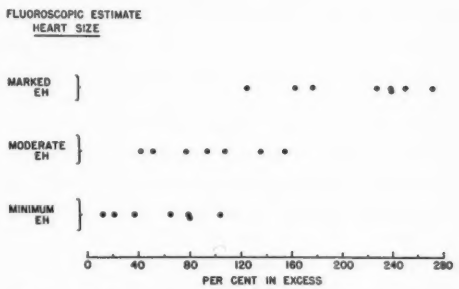

FIG. 2. Comparison of fluoroscopic estimate of cardiac enlargement and heart weight for 22 patients (per cent excess of heart weight over expected heart weight for sex and body weight).

Autopsies were performed in 25 of the 78 deaths. Six autopsied patients had carditis clinically; it was confirmed in all. No other instances of carditis were found at autopsy. In 22, death was directly attributable to rheumatic heart disease or its complications. In all instances of mitral stenosis the clinical diagnosis was confirmed pathologically and no false positive diagnoses were made clinically. A failure in clinical diagnoses was noted in 2 instances of aortic insufficiency, 2 of aortic stenosis, and 4 of tricuspid stenosis. Two patients had mitral insufficiency alone, both of whom died of noncardiac causes. There were 9 patients with mitral stenosis and insufficiency alone, and 15 with mitral and aortic disease; 5 of the latter group had tricuspid insufficiency.

These autopsies were performed between the years 1937 to 1954, and only 19 were performed at the New York Hospital. In 22, data were available with reference to heart weight, and in 21 direct measurements were made of the thicknesses of both ventricles. Figure 2 shows a good correlation between the fluoroscopic estimate of over-all heart size and the per cent in excess of actual, over expected, heart weight when corrected for body weight and sex.[6] The heart weights ranged between 270 and 1,010 Gm. Among 21 patients with left ventricular enlargement fluoroscopically, hypertrophy was noted in 16 at autopsy. In 11 patients enlargement of the right ventricle was demonstrated fluoroscopically and in 6 of these hypertrophy was reported pathologically.

Ten patients had electrocardiograms demon-

strating atrial fibrillation, all of whom had fluoroscopic evidence and 7 of whom had autopsy evidence of left atrial enlargement. Inasmuch as the majority of these patients died prior to the use of unipolar leads, no statement can be made as to the relationship between electrocardiographic and postmortem evidence of specific chamber hypertrophy.

Discussion

It is significant that 89 per cent of the 385 patients with rheumatic heart disease, ranging in age from 20 to 49 years, who were under our medical supervision were asymptomatic. It is to be recalled that the anatomic diagnosis was established in the majority by age 20, and that these patients were under observation because of a long-term follow-up. Of interest is the observation that one half of these patients had simple mitral insufficiency without marked cardiac enlargement. None of these asymptomatic patients would, as of the present time, be considered candidates for cardiac surgery.

Of particular importance is the finding that only 45 patients with mitral stenosis and insufficiency alone or associated with aortic valvular disease had cardiopulmonary symptoms. This small percentage of the total would thus constitute a group comparable to the type of patients presenting themselves for surgical consideration. The 173 with mitral insufficiency were asymptomatic. Of the total 161 patients with mitral stenosis and insufficiency, 27 had symptoms. Eighteen of the 51 with mitral stenosis and insufficiency and aortic valvular disease were symptomatic. It is notable that the majority of these patients had marked cardiac enlargement, constituting two thirds of those with mitral stenosis alone, and three fourths of those with associated aortic disease. The greater proportion of these patients were in the fourth and fifth decades of life.

It should be emphasized that progressive cardiac enlargement was not observed with advancing age alone in either the symptomatic or asymptomatic group. There is thus no evidence from these data that valvular deformity per se was a major factor contributing to degree of cardiac enlargement. Morbidity, like mortality, would appear to be more closely related to degree of cardiac enlargement than to type of valvular lesions.

The observation that some patients in the asymptomatic group revealed a diminished vital capacity is worthy of comment. We suggest that these patients may have been unaware of abnormal symptoms. In some, decreased vital capacity may have been related to reduced pulmonary elasticity. It is of interest that the patients in functional class II who were symptomatic had vital capacities within their normal limits. It is likely that the subjective complaints may not have been organic in origin.

In the analysis of changes in morbidity, it was apparent that a common factor was the occurrence of demonstrable carditis in both the living and in those who died. Also of importance was the occurrence of atrial fibrillation, subacute bacterial endocarditis, and thromboembolism. In others, with associated illnesses such as pneumonia and the occurrence of atrial fibrillation, the presence of subacute carditis could not be excluded.

The small number of patients in this study who were symptomatic renders difficult any over-all statement as to indications for surgery. However, these patients are probably representative of those for whom surgical intervention is considered. An inspection of our data reveals that the outstanding factors inducing progressive disability are not amenable to surgical correction; specifically, carditis, atrial fibrillation, thromboembolism, and marked cardiac enlargement. The removal of thrombi from a dilated atrium would probably reduce morbidity and mortality consequent upon thromboembolism. It is possible in some cases that surgical reduction of interatrial pressure might decrease the incidence of fibrillation. Since the majority of symptomatic patients were in the fourth and fifth decades of life, one could speculate that asymptomatic patients may be considered for surgical prophylactic therapy early in the third decade.

Summary

The natural morbidity experienced by 385 children with rheumatic heart disease, reaching the ages of 29 to 49 years, is presented. One

hundred fifty-seven patients were in the third decade of life, 176 in the fourth, and 52 in the fifth decade. The anatomic diagnosis was established in the majority by the age of 20 years: mitral insufficiency in 173 patients, mitral stenosis and insufficiency in 161, and 51 patients had aortic and mitral valvular lesions. All of the 173 patients with mitral insufficiency were asymptomatic. Cardiac enlargement was minimal or moderate. Of 161 patients with mitral stenosis and insufficiency, 27 (17 per cent) had cardiopulmonary symptoms. About two thirds of these had marked cardiac enlargement. Of 51 patients with combined aortic and mitral valvular lesions, 18 or about one third had cardiopulmonary symptoms; 14 of these had marked cardiac enlargement. Three hundred forty (89 per cent) patients were asymptomatic, and 45 (11 per cent) experienced cardiopulmonary symptoms.

The factors found responsible for morbidity and mortality after the age of 20 were active carditis, atrial fibrillation, bacterial endocarditis, pregnancy, pneumonia, and embolic phenomena.

Patients who experienced cardiopulmonary symptoms had been asymptomatic for periods of 2 to 24 years after age 20, with an average of 10.5 years. Patients who died of cardiac causes had been asymptomatic for 1 to 20 years before the terminal event.

Cardiac chamber enlargement did not appear to progress with advancing age per se, irrespective of the type of valvular deformity. Confirmation of fluoroscopic estimate of over-all heart and chamber enlargement was obtained on postmortem examination.

The majority of patients with rheumatic heart disease who survived to the age of 20 to 49 years were in functional classification I. The majority of patients with mitral stenosis and insufficiency alone or with associated aortic disease who had markedly enlarged hearts were in functional classification II, III, or IV.

The residual cardiac damage sustained in the first 2 decades of life, particularly the extent of cardiac enlargement, appears to be the major factor influencing morbidity and mortality in the third, fourth, and fifth decades.

Summario in Interlingua

Es presentate datos in re le morbiditate natural experientiate per 385 patientes pediatric con rheumatic morbo cardiac qui attingeva un etate de inter 29 e 49 annos. Cento cinquanta-septe del patientes esseva in le tertie decennio de lor vitas al tempore del studio; 176 esseva in le quarte; e 52 esseva in le quinte. Le diagnose anatomic esseva establite in le majoritate del casos ante le etate de 20 annos: Insufficientia mitral in 173 patientes, stenosis e insufficientia mitral in 161, e lesiones del valvulas aortic e mitral in 51. Omne le 173 patientes con insufficientia mitral esseva asymptomatic. Le allargamento cardiac esseva minimal o moderate. Ex le 161 patientes con stenosis e insufficientia mitral, 27 habeva symptomas cardiopulmonar (17 pro cento). Circa duo tertios de istes habeva marcate grados de allargamento cardiac. Ex le 51 patientes con combinate lesiones del valvulas aortic e mitral, 18 o circa un tertio habeva symptomas cardiopulmonar. Dece-quatro de istes habeva marcate grados de allargamento cardiac. Tres centos quaranta patientes (89 pro cento del serie total) esseva asymptomatic, e 45 (11 pro cento) experientiava symptomas cardiopulmonar.

Le factores recognoscite como responsabile pro morbiditate e mortalitate post le etate de 20 annos esseva carditis active, fibrillation atrial, endocarditis bacterial, pregnantia, pneumonia, e phenomenos embolic.

Patientes qui experientiava symptomas cardiopulmonar habeva essite asymptomatic durante periodos de inter 2 e 24 annos post passar le etate de 20 annos. Le duration medie de iste periodo asymptomatic esseva 10,5 annos. Patientes qui moriva ab causas cardiac habeva essite asymptomatic durante inter 1 e 20 annos ante le evento terminal.

Allargamento de camera cardiac non pareva progreder con le progresso del etate per se, sin reguardo al typo de deformitate valvular. Le estimation fluoroscopic del allargamento del corde in general e del cameras individual esseva confirmate per examines necroptic.

Le majoritate del patientes con rheumatic morbo cardiac attingente etates de inter 20 e

49 annos esseva functionalmente in le classification I. Le majoritate del patientes con stenosis e insufficientia mitral sin o con associate morbo aortic sed con marcate grados de allargamento cardiac esseva functionalmente in le classificationes II, III, o IV.

Le residue insulto cardiac experientiate durante le 2 prime decennios del vita—specialmente le grado del allargamento cardiac—es apparentemente le major factor de influentia super le morbiditate e mortalitate durante le tertie, quarte, e quinte decennios.

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FORTHCOMING ARTICLES

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Effect of Sitosterol on the Concentration of Serum Lipids in Patients with Coronary Atherosclerosis

By FLETCHER P. RILEY, M.D., AND ALFRED STEINER, M.D.

The oral administration of large amounts of sitosterol to patients with coronary atherosclerosis has resulted in statistically significant decrease in serum cholesterol in one half of the trial periods. However, because of the fluctuation of the serum cholesterol that occurs in patients with coronary atherosclerosis, further study will be necessary to demonstrate that the decrease in serum cholesterol coincident with sitosterol administration is not due to the lability of the serum lipids in this group of individuals.

THERE are conflicting reports in the literature concerning the effect of plant sterols on serum lipid concentrations. Pollack[1] in 1953 reported that 5 to 10 Gm. of a sitosterol mixture (prepared from soybeans) given orally daily for 7 to 28 days caused a fall in serum cholesterol in 24 of 26 patients. Best et al.[2, 3] in 1954 and 1955 found that the feeding of 20 to as much as 50 Gm. of sitosterol daily to 14 ambulatory patients during study periods of 13 to 64 weeks resulted in a mean fall in serum cholesterol values of 16 per cent in 12 "hypercholesterolemic" subjects and of 6.8 per cent in 2 "normocholesterolemic" subjects. The falls in serum cholesterol were accompanied by decreases in total serum lipid and serum neutral fat. Joyner and Kuo[4] reported significant decreases in serum cholesterol within a week or more upon the oral administration of 12 to 24 Gm. of β-sitosterol suspension to both "normocholesterolemic" and "hypercholesterolemic" patients. They found no significant effect when the dosage was less than 10 Gm. a day. Farquhar, Smith, and Dempsey[5] recorded significant lowering of serum cholesterol and β-lipoprotein lipid concentrations in 11 of 15 hospitalized patients with coronary atherosclerosis after the oral administration of 12 to 18 Gm. of β-sitosterol for periods of 12 to 24 weeks. In a recent article, Barber and Grant[6] reported a suggestive fall in serum cholesterol in 24 of 26 subjects receiving 9 Gm. of β-sitosterol daily. In these 24 patients there was a reduction in the minimal serum cholesterol level under the sitosterol regimen, but in only 17 was the mean level lowered. However, in a footnote to the article, without presentation of data, these workers stated that a significant decrease in serum cholesterol occurred when the daily amount of sitosterol was increased from 9 to 18 Gm. Wilkinson and his co-workers,[7, 8] however, reported that the oral administration of 15 to 30 Gm. of γ-sitosterol daily for 3 to 35 weeks failed to alter the serum cholesterol in 7 patients.

The present report summarizes a 16-month study on the changes in serum lipid concentrations during the oral administration of sitosterol to 13 patients with coronary atherosclerosis.

METHOD

Seven hospitalized and 6 ambulatory patients composed the clinical group. Among the hospitalized patients, 4 of the 7 had historical and electrocardiographic evidence of coronary atherosclerosis and myocardial infarction; 1 (HB) had primary myxedema with clinical and electrocardiographic evidence of coronary atherosclerosis; and the remaining 2 (JAK and EL) had angina pectoris and hemiplegia believed to be due to cerebral thrombosis.

In the ambulatory group, 3 of the 6 patients had coronary insufficiency apparently related to coronary atherosclerosis. The remaining 3 patients had the same syndrome in association with xanthomatosis.

The sitosterol utilized in the study consisted of a 20 per cent liquid suspension of mixed β-sitosterol

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and dihydro-β-sitosterol.* It was administered orally before each of the 3 daily meals in divided dosages totaling 19 to 52.5 Gm. per day. The periods of sitosterol administration were alternated in the hospitalized subjects with similar periods of a placebo preparation of the same appearance, consistency, and taste as the sitosterol. The patients were not informed that a placebo preparation was being utilized. The period of sitosterol administration varied from 1 to 6 months per patient. A 1- to 4-month control period preceded the sitosterol-feeding period in each subject.

All of the hospitalized subjects were maintained on the regular hospital diet of approximately 2700 calories, containing 50 to 60 Gm. of fat. In 1 patient (HL) dietary sodium was restricted to not more than 1.5 Gm. pre day. The diet of the ambulatory subjects was not regulated as to amount or type.

Serum for blood lipid values was obtained in the fasting state biweekly in the hospitalized patients and 2 to 4 times per month in the ambulatory group. Total serum cholesterol was determined by the method of Schoenheimer and Sperry[9] or the method of Abell et al.,[10] both of which give comparable results in this laboratory. The lipid phosphorus was determined by the method of Fiske and SubbaRow[11]; total lipid by a gravimetric procedure; and the neutral fat was calculated from the formula: $N.F. = Total\ Lipid - [(1.5 \times Tot.\ chol.) + Lipid\ Phos. \times 25 + 200]$. Electrocardiograms were obtained at least once monthly. Liver function studies were made during control and experimental periods. Weights were recorded at weekly or bimonthly intervals.

Results

The results have been summarized by dividing the 13 patients into 2 groups; the first consisting of 10 patients with coronary atherosclerosis and the second of 3 patients with coronary atherosclerosis and associated xanthomatosis. As indicated in table 1 there were 18 periods of sitosterol feeding in the 10 patients comprising the first group. A mean fall in serum total cholesterol was demonstrated in all subjects on at least 1 of the dosages of sitosterol given. In 17 of the 18 sitosterol therapy periods, the average serum total cholesterol was lower than the preceding control or placebo value. However, in only 9 of the 18 periods was this decrease statistically significant ($p \leqq .01$).

* β-dihydro-β-sitosterol = Cytellin, an Eli Lilly product kindly made available for this study by Dr. R. E. Shipley of the research division of that company.

Table 1.—*Effect of β- and Dihydro-β-Sitosterol on Average Serum Total Cholesterol (mg./100 ml.)*

	Placebo or control	Sitosterol	*p*	Daily dosage (Gm.)
Hospital subjects				
HB	358	351	1.00	37.5
JAK	286	270	.02	52.5
	314	295	.02	37.5
JK	222	235	.04	19
	226	206	<.001	37.5
		200	<.001	52.5
	211	—	.40*	
EL	247	230	<.001	37.5
	287	—	<.001*	
HL	247	232	<.001	37.5
		216	<.001	52.5
AM	285	253	<.001	52.5
	269	262	.70	37.5
	285	—	1.00*	
SS	284	261	.05	19
	275	257	.01	37.5
		257	.01	52.5
	293	286	1.00	37.5
	327	—	<.001*	
Ambulatory subjects				
JM	236	203	.001	19
MH	250	234	.06	19
JP	259	246	.05	19

* *p* Final control values as compared to initial control values. In 9 of 18 sitosterol feeding periods $p < 0.001$.

There were 9 periods of placebo administration in the hospitalized patients. The serum cholesterol returned toward values not significantly different from the initial control in 6 instances; however, in 3 patients the average serum total cholesterol in the final placebo or control period was significantly higher than the initial control (JAK, AS, EL).

In table 2 the mean serum total cholesterol for the entire sitosterol feeding period has been paired with the initial control value for each of the 10 subjects. It can be seen that in only 5 of the 10 patients was there a statistically significant depression of the mean serum total cholesterol during sitosterol administration as compared to the initial control values. Figure 1 shows the effect of β-sitosterol and the placebo on the serum lipid pattern of patient SS. The mean fall in serum total cholesterol for all 10 subjects was 6.6 per cent (17 mg. per cent)

TABLE 2.—*Effect of β- and Dihydro-β-Sitosterol on Average Serum Total Cholesterol (mg./100 ml.)*

	Initial control	Standard error of mean	Number of determinations	Sitosterol	Standard error of mean	Number of determinations	p	Daily dosage (Gm.)	Weeks on sitosterol
Hospital subjects									
HB	358 ± 22	5.5	16	351 ± 26	9.2	8	1.00	37½	4
JAK	286 ± 17	5.3	10	287 ± 14	2.4	33	1.00	37½–52½	24
JK	222 ± 20	5.9	12	207 ± 9	1.7	28	.02	17–52½	15
EL	247 ± 13	3.6	13	230 ± 12	2.7	20	<.001	37½	14
HL	247 ± 10	3.1	10	227 ± 14	2.9	23	<.001	37½–52½	13
AM	285 ± 18	5.3	12	256 ± 12	2.7	20	<.001	37½–52½	10
AS	284 ± 24	5.4	19	266 ± 14	2.3	38	.002	19–52½	22
Ambulatory subjects									
MH	250 ± 15	6.3	6	234 ± 13	5.4	6	.06	19	8
JM	236 ± 17	6.0	8	203 ± 13	4.3	9	<.001	19	12
JP	259 ± 5	2.2	6	246 ± 12	5.5	5	.05	19	8

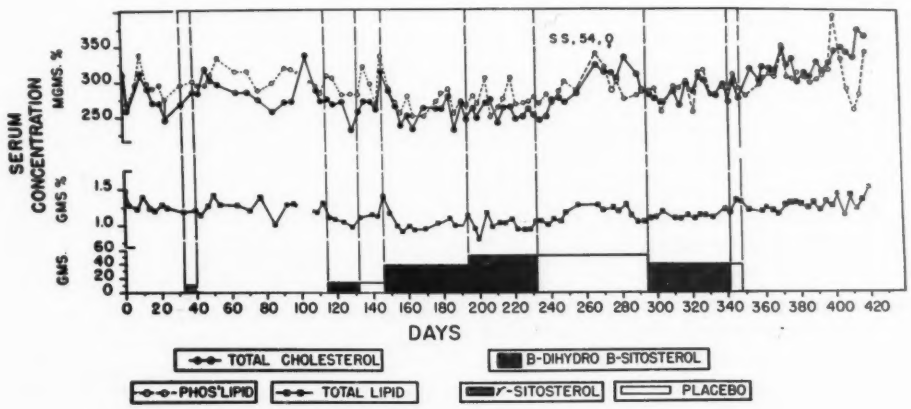

FIG. 1. Effect of β-Dihydro-β-Sitosterol on serum lipid pattern.

with a range of 0 to 14 per cent (+12 to −33 mg. per cent). The mean fall in serum total cholesterol for the 5 subjects in whom the depression was statistically significant was 9 per cent (23.4 mg. per cent) with a range of 7 to 14 per cent (17 to 33 mg. per cent).

Table 3 depicts the changes in total serum lipid concentration during the study. The total lipid concentration fell significantly in 5 of the 10 patients during the course of sitosterol administration as compared to the initial control value. Where placebo was administered, this fall was maintained during placebo as well as during the period of sitosterol feeding. In 2 of 10 patients, however, the mean total lipid rose significantly higher than the initial control value (EL and JAK); and in the remaining 3 of the 10, there was no significant change in total lipid. The average fall during the experimental period on sitosterol as compared to the initial control was 9 per cent with a range of +5 to −20 per cent.

The serum concentration of neutral fat fell consistently throughout both placebo and sitosterol administration periods in 7 of the 10 subjects, and rose in the remaining 3 (table 4). The average fall in serum neutral fat during sitosterol feeding as compared to the initial control was 25 per cent with a range of −60 to +100 per cent. The variation in the indi-

TABLE 3.—*Effect of β- and Dihydro-β-Sitosterol on Average Total Serum Lipid Concentration (Gm./100 ml.)*

	Placebo or control	Sitosterol	*p*
Hospital subjects			
HB	1.47	1.35	.01
JAK	1.15	1.11	.25
	1.23	1.32	.04
JK	0.82	0.82	1.00
	0.78	0.73	.40
		0.72	.22
	0.74	—	.001*
EL	0.98	0.94	.50
	1.08	—	.001*
HL	0.93	0.85	<.001
		0.82	<.001
AM	0.98	0.98	1.00
	0.97	1.03	.10
SS	1.26	1.07	.001
	1.17	1.01	.01
		0.99	.01
	1.14	1.11	.50
Ambulatory subjects			
MH	1.00	0.94	.70
JM	1.07	0.93	.001
JP	0.99	1.00	1.00

* As compared to initial control.

TABLE 4.—*Effect of β- and Dihydro-β-Sitosterol on Average Neutral Fat (mg./100 ml.)*

	Placebo or control	Sitosterol
Hospital subjects		
HB	394	283
JAK	247	239
	289	379
JK	73	52
	35	47
		41
	37	—
EL	115	131
	154	
HL	118	87
		81
AM	92	147
	103	182
	100	—
SS	327	181
	256	148
		131
	203	186
Ambulatory subjects		
MH	163	148
JM	258	188
JP	243	181

vidual neutral fat values was so great that in general a mean change of less than 30 per cent tended to be statistically insignificant.

The serum phospholipid concentration tended to vary proportionately with the serum total cholesterol, such that the C/P ratio did not change appreciably except in the final control period of 2 of the 10 patients (AS and EL) in whom the C/P ratio was significantly higher than in the initial control.

During the course of the study there was no significant change in weight or in liver function values (serum proteins, cephalin flocculation, thymol turbidity, and Bromsulphalein retention) in these 10 patients. There was no significant alteration in the clinical course or development of febrile episodes in any patient except one. In SS there was evidence of progression in myocardial damage during both sitosterol and placebo administration periods, as well as the occurrence of pulmonary infarction. In no instance was there evidence of clinical benefit from sitosterol administration as judged by incidence of chest pain or improvement in the electrocardiogram.

All 3 patients with coronary atherosclerosis and associated xanthomatosis exhibited falls in serum total cholesterol during the sitosterol feeding period (table 5). However, in each instance, after 6 to 9 weeks on sitosterol, the serum cholesterol rebounded towards control levels (fig. 2). This was reflected in the mean change in that the mean serum total cholesterol during sitosterol administration was statistically significantly lower than the initial control value in only 2 of the 3 patients (CK and WF). The mean fall in serum total cholesterol for the group during sitosterol administration was 12 per cent (66.5 mg. per cent) with a range of 6 to 22 per cent (32 to 81 mg. per cent).

In this group the total lipid did not change significantly during sitosterol administration and in 2 of the 3 (CK and WF) the neutral fat tended to rise during sitosterol administration.

TABLE 5.—*Effect of β- and Dihydro-β-Sitosterol on Concentration of Serum Lipids*

Subjects with xanthomatosis	Initial control	Standard error of mean	Number of determinations	Sitosterol	Standard error of mean	Number of determinations	p	Daily dosage (Gm.)	Weeks on sitosterol
Mean Cholesterol (mg./100 ml.)									
CK	507 ± 25	12.5	4	431 ± 48	20	6	.003	20	12
WF	363 ± 5	3.5	2	282 ± 52	17	9	<.001	37½	19
GP	563 ± 18	7.5	6	531 ± 43	13.4	10	.04	37½	19
Mean Total Lipid (Gm./100 ml.)									
CK	1.59 ± .02	.01	2	1.56 ± .07	.03	6	1.00		
WF	1.44 ± .03	.02	2	1.38 ± .36	.12	9	1.00		
GP	1.75 ± .11	.05	6	1.66 ± .12	.04	10	.19		
Mean Neutral Fat (mg./100 ml.)									
CK	266			311					
WF	347			463					
GP	280			281					
Mean C/P Ratio									
CK	1.38			1.17			.001		
WF	1.07			0.99			.001		
GP	1.34			1.38			1.00		

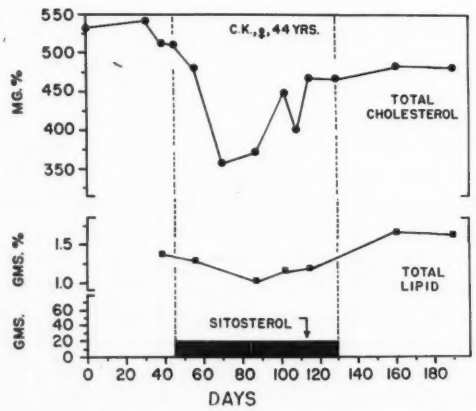

FIG. 2. Effect of sitosterol feeding on serum lipids in patient with xanthomatosis.

The cholesterol/phospholipid ratio fell significantly in 2 patients (CK and WF) and did not change in a third.

In 1 patient, WF, the xanthomatous lesions became smaller and less firm when the serum cholesterol levels became lower.

DISCUSSION

The results of this study indicate that the feeding of sitosterol to patients with atherosclerosis results in a lowering of the serum cholesterol level. However, this decrease is statistically significant in only one half of the trial periods. A previous report[12] from this laboratory has shown that the serum cholesterol level in patients with coronary atherosclerosis is inconstant and varies widely. The standard deviation of the mean serum cholesterol values of the patients with coronary atherosclerosis was almost 3 times the standard deviation of the control subjects. The difference between the mean serum cholesterol levels of any given control period and a treatment period should approximate 10 per cent in order to have statistical significance. For this reason borderline alterations in serum cholesterol ascribed to a therapeutic program must be highly suspect, even though on statistical analyses the differences are significant.

From a clinical view point the lowering of the serum cholesterol levels in the patients with atherosclerosis in this study was probably not of such a degree as to be likely to alter their clinical course. In 1 patient, SS, a mild bout of coronary insufficiency occurred during the period of sitosterol ingestion. In the patients with xanthomatosis the lowering effect of sitosterol on the serum lipids was more marked but only

transitory. After 6 to 9 weeks the serum cholesterol level in each of the subjects started returning to the control levels. However, in 1 of the patients the skin lesions became smaller during the time of reduced serum cholesterol levels.

It would appear that the results reported in this article are at variance with those reported by other workers. However, a closer examination of these studies does not reveal any great differences. In an article by Farquhar et al.[5] on 15 patients with coronary atherosclerosis who were fed 12 to 18 Gm. of sitosterol daily, the authors reported highly significant reductions in serum cholesterol. In a statistical analysis of the data the authors found that in only 5 of the 15 subjects was the decrease in serum cholesterol of such an extent as to result in a $p < 0.001$. In the remaining 10 patients the statistical analysis revealed the p value to vary from 0.01 to 0.5. In the study by Best and his co-workers[3] it was concluded that a sustained fall in serum cholesterol occurred in association with sitosterol feeding. These authors did not subject their data to statistical analysis. However, the average of the mean falls in serum cholesterol for all of the 14 patients was 14.5 per cent. In 7 of the 14 patients the decrease in mean serum cholesterol did not appear to be significant. The studies by Wilkinson et al.[7, 8] reported no significant decreases in serum cholesterol as the result of sitosterol ingestion. It would appear that further studies are necessary in order to demonstrate that the lowering effect of sitosterol on serum cholesterol is significantly greater than the variation in serum cholesterol levels encountered in patients with coronary atherosclerosis.

Summary

A colloidal suspension containing from 19 to 52.5 Gm. per day of β- and dihydro-β-sitosterol was administered orally to 13 patients with coronary atherosclerosis, 3 of whom had associated xanthomatosis. The serum total cholesterol concentration decreased during the 1- to 6-month periods of sitosterol ingestion. However, in only 9 of 18 instances of sitosterol administration in the 10 patients with coronary atherosclerosis was this fall in serum cholesterol statistically significant. In the 3 patients with xanthomatosis and coronary atherosclerosis, the serum cholesterol level fell significantly but rebounded toward control values after 6 to 9 weeks, despite the maintenance of the sitosterol regimen. The fall in mean serum total cholesterol during sitosterol feeding was more impressive in this latter group in which the initial serum total cholesterol values were higher. The effect on the neutral fat and total lipid levels of the serum was variable. The cholesterol/phospholipid ratio tended to remain unchanged throughout the study. Results obtained in this clinical study indicate that further observations are necessary in order to demonstrate that the fall in serum cholesterol coincident with sitosterol ingestion is greater than the fluctuation of the serum cholesterol levels that occur in patients with coronary atherosclerosis.

Summario in Interlingua

Ab 19 a 52,5 g per die de beta- e bihydro-beta-sitosterol in un suspension colloidal esseva administrate per via oral a 13 patientes con atherosclerosis coronari, incluse 3 con xanthomatosis associate. Le concentration seral de cholesterol total descendeva durante le periodos de inter 1 e 6 menses de ingestion de sitosterol. Tamen, in le 10 patientes con atherosclerosis coronari, iste reduction del cholesterol seral esseva statisticamente significative in solmente 9 ex 18 administrationes de sitosterol. In le 3 patientes con xanthomatosis e atherosclerosis coronari, le nivello de cholesterol seral descendeva significativemente sed remontava al valores de controlo post 6 a 9 septimanas in despecto del continuation del regime a sitosterol. Le reduction del nivello medie del cholesterol total in le sero durante le ingestion de sitosterol esseva plus impressionante in le secunde gruppo, in que le valores initial de cholesterol total in le sero habeva essite plus alte. Le effectos super le nivellos de grassia neutre e de lipido total del sero esseva variabile. Le proportion de cholesterol a phospholipido tendeva a remaner sin alteration durante le periodo del studio. Le resultatos obtenite in iste studio clinic indica que observationes additional es

necessari pro demonstrar que le reduction del cholesterol del sero occurrente in coincidentia con le ingestion de sitosterol es plus grande que le fluctuationes del nivellos de cholesterol seral que occurre in patientes con atherosclerosis coronari.

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Albert, S. N., Spencer, W. A., Boling, J. S., and Thistlethwaite, J. R.: Hypothermia in the Management of the Poor-Risk Patient Undergoing Major Surgery. J.A.M.A. **163:** 1435 (April 20), 1957.

Observations in 76 patients of various ages are described briefly. Hypothermia of 28 to 32 C. was achieved in each by using a water-cooled mattress and infusing trimethaphan camphorsulfonate (Arfonad). Less anesthesia was required and surgery was better tolerated by the cooled individual. Intra- and postoperative adrenal cortical response was less as indicated by a smaller rise in the plasma level of 17 hydroxycorticosteroids, greater urinary sodium loss and greater diuresis of a water load. Ventricular irritability increased and premature contractions appeared in over one half of the patients; trimethaphan administration suppressed this disturbance. Hypothermia is advocated as a protective adjunct in the major surgical management of the poor-risk person.

ROGERS

Hemodynamic Aspects of Diffuse Myocardial Fibrosis

By EUGENE D. ROBIN, M.D., AND C. SIDNEY BURWELL, M.D.

The circulatory changes associated with diffuse myocardial fibrosis have been studied in 11 patients. The characteristics of this form of congestive failure and its similarities to those manifested by constrictive pericarditis and endocardial fibroelastosis are discussed.

MYOCARDIAL fibrosis is defined as a diffuse replacement or invasion of the myocardium by fibrous connective tissue to such an extent that there is interference with the action of the heart.

Eleven patients with this disorder have been studied. The purpose of this paper is to report the hemodynamic findings in these patients as studied by various standard methods including right heart catheterization. The changes in the circulation associated with diffuse myocardial fibrosis have not previously been studied in these ways. Aspects other than pathologic physiology will be reported in a subsequent communication.[1]

MATERIAL AND METHODS

In 9 of the 11 patients an exploratory thoracotomy revealed a normal pericardium and a grossly diseased myocardium. In 3 of these the diagnosis of myocardial fibrosis was confirmed by microscopic study. In one patient (D.S.) neither operative nor postmortem proof of myocardial fibrosis was available. However, the clinical findings were so clear-cut that inclusion in this series seems warranted. In another patient (E.F.) myocardial fibrosis had developed in association with constrictive pericarditis. Despite surgical relief of the pericardial restriction, this patient eventually died of congestive heart failure. Postmortem examination revealed myocardial fibrosis resulting from involvement of the myocardium by the inflammatory process that had produced constrictive pericarditis. This type of myocardial involvement is frequent in patients with constrictive pericarditis.[2]

Data relating to the age of the patient, manifestations, and etiology are listed in table 1. The recorded etiologic antecedent of the fibrosis in each patient is the best judgment that could be reached with the evidence available.

TABLE 1.—*Clinical Data in Patients with Myocardial Fibrosis Manifested by Intractable Right and Left Heart Failure*

Patient	Age	Etiologic basis of fibrosis	Diagnosis made by:
W. L.	38	Coronary artery disease	Operation and postmortem examination
L. H.	39	Unknown	Operation
R. C.	37	Unknown	Operation
E. F.	44	Tuberculosis	Operation and postmortem examination
G. S.	39	? Old myocarditis	Postmortem examination
N. L.	15	Old myocarditis	Operation and postmortem examination
F. O'C.	56	Coronary artery disease	Operation
Wm. Wa.	58	Unknown	Operation
M. I.	44	Unknown	Operation
Wm. Wo.	54	Coronary artery disease	Operation
D. S.	48	Unknown	Clinical picture

Cardiac catheterization was performed with the patient at rest. No sedative was administered. The catheter was introduced by way of a vein in the antecubital space and manipulated until the tip occluded a branch of the pulmonary artery. Pulmonary "capillary" pressure was recorded.[3] The catheter tip was then withdrawn to a point slightly distal to the bifurcation of the pulmonary artery. At this time a short-bevel needle (20- or 21-gage) was inserted into the brachial artery. The lumen of this needle was kept patent by a slow infusion of saline solution. The patient's expired air was collected for a 3-minute period in a Douglas bag and midway during this collection samples of blood were withdrawn simultaneously from the brachial and pulmonary arteries. Pressures were then recorded

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TABLE 2.—*Volumes of Blood Flow and Related Data in Patients with Myocardial Fibrosis*

Name	Body surface area (M.²)	O_2 consumption (ml./min.)	O_2 saturation (%)	A-V O_2 difference (ml./L.)	Cardiac output (L./min.)	Heart rate/min.	Cardiac index (L./min./M.²)	Stroke index (ml./beat/M.²)	Stroke output (ml./beat)	Output per 100 ml. O_2 (L./min.)	Rhythm
W. L.	1.67	189	95	75	2.5	80	1.50	19.0	32	1.4	NSR*
L. H.	1.83	221	87	69	3.2	72	1.70	24.0	44	1.4	NSR
R. C.	1.54	198	97	49	4.0	71	2.60	37.0	57	2.0	AF†
E. F.	2.00	278	99	58	4.8	71	2.40	31.0	62	1.7	NSR
G. S.	1.81	324	97	63	5.1	110	2.84	26.0	47	1.6	NSR
N. L.	1.18	152	96	58	2.6	100	2.20	22.0	26	1.6	AF
F. O. C.	1.85	268	96	125	2.1	86	1.10	9.5	18	0.8	AF
Wm. Wa.	1.86	320	99	60	5.3	57	2.90	50.0	93	1.7	AF
M. I.	2.10	—	94	—	—	72	—	—	—	—	AF
Wm. Wo.	1.96	303	98	64	4.7	100	2.40	24.0	47	1.6	NSR
D. S.	1.70	197	98	100	2.0	95	1.20	12.0	21	1.0	NSR

* Normal sinus rhythm. † Atrial fibrillation.

TABLE 3.—*Pressures and Related Data in Patients with Myocardial Fibrosis*

Name	Peripheral venous mean (mm. Hg)	Right atrial mean (mm. Hg)	Right ventricular (mm. Hg)		Pulmonary artery (mm. Hg)			Pulmonary "Capillary" mean (mm. Hg)	Brachial artery (mm. Hg)			Pressure plateau	Diastolic dip
			Syst.	Diast.	Syst.	Diast.	Mean		Syst.	Diast.	Mean		
W. L.	38	40	75	40	75	42	53	40	115	80	92	present	present
L. H.	16	16	23	15	20	10	16	15	110	80	90	present	present
R. C.	16	14	25	13	24	13	18	13	129	73	95	present	present
E. F.	16	15	40	17	37	22	27	20	124	96	103	present	present
G. S.	15	16	60	15	62	32	42	39	110	80	90	absent	absent
N. L.	16	14	52	26	51	29	39	27	90	65	73	absent	present
F. O'C	24	24	67	26	74	41	50	37	106	70	82	absent	present
Wm. Wa.	18	18	46	24	53	22	32	33	103	70	90	absent	present
M. I.	27	23	—	—	40	22	32	—	125	83	105	absent	—
Wm. Wo.	16	16	mean = 16		40	10	24	25	135	85	101	absent	—
D. S.	18	17	63	27	61	39	50	35	130	100	107	absent	present

in these arteries, the catheter tip was withdrawn and pressures were recorded in the right ventricle, the right atrium, and the superior vena cava successively.

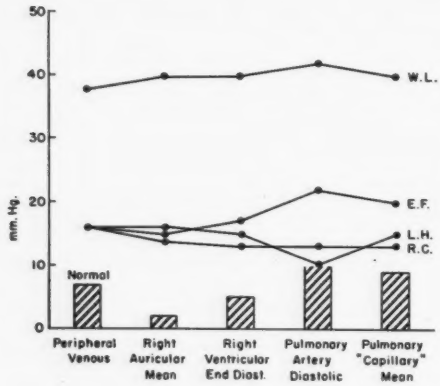
The volume of air expired in the 3-minute period was measured in a Tissot spirometer and the concentration of oxygen was determined by a Pauling oxygen analyzer. A respiratory quotient of 0.82 was assumed, and appropriate correction was made for the change in nitrogen concentration in the expired air.[4] The oxygen content and oxygen capacity of the blood samples were determined by the method of Van Slyke and Neill.[5] All pressure measurements were made by means of a Sanborn electromanometer recording on a multichannel direct-writing oscillograph. Mean pressures were obtained by electric integration. The zero point for pressure measurements was 10 cm. anterior to the back with the patient supine.[6] Cardiac output was calculated by the Fick equation.[7]

RESULTS

Volumes of blood flow and related data are shown in table 2. Cardiac outputs varied from 2.0 to 5.3 L. per minute. The customary derivatives of cardiac output (cardiac index, stroke output, and stroke index) were found to be low. To relate the output to actual oxygen consumption instead of to body surface area, the cardiac output per 100 ml. absorbed oxygen has been calculated. In every patient this was below the expected figure of 2.00.

Five patients had atrial fibrillation, the rest had normal sinus rhythm.

The height and contour of pressure curves in various parts of the circulatory system are shown in table 3. These data are summarized as follows:



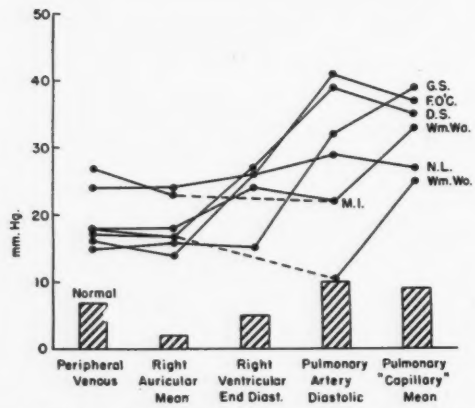


FIG. 1 *Top.* Intravascular pressures in 4 patients showing a plateau of the "biventricular" type.

FIG. 2 *Bottom.* Intravascular pressures in 7 patients showing the absence of a plateau in the "left ventricular" group.

1. Every patient showed a definite elevation of pressures in the pulmonary "capillaries," the pulmonary artery, the right ventricle, the right atrium and the peripheral veins.*

2. These patients can be divided into 2 groups:

(a) *The "biventricular" group.* Four patients (W. L., L. H., R. C., E. F.) showed a plateau of pressures from the peripheral veins to the pulmonary "capillaries." In these patients the mean pressure in the peripheral veins, the right atrium, the end-diastolic pressure in the right ventricle, the diastolic pressure in the pulmonary artery, and the mean pressure in the pulmonary "capillaries" did not differ by more than 5 mm. Hg (fig. 1). Since these pressures indicated abnormal function of both ventricles this group of patients is referred to as the "biventricular" group. Postmortem studies done on 2 of the patients (W. L., E. F.) who exhibited pressure plateaus showed myocardial fibrosis involving both ventricles.

(b) *The "left ventricular" group.* In 7 patients (G. S., N. L., F. O'C., Wm. Wa., M. I., Wm. Wo., D. S.) the pressures relating to the function of the left side of the heart (i.e., pulmonary "capillary" and pulmonary artery pressures) exceeded the pressures in the peripheral veins and the right atrium by at least 5 mm. Hg (fig. 2). Therefore, a plateau was not present. Two of these 7 patients (G. S., N. L.) have had postmortem examinations. Both showed predominant fibrosis of the left ventricle with relative sparing of the right. The significance of these 2 groups is discussed later in this paper.

3. Pressures in the systemic arteries were within normal limits in all patients.

4. Eight out of 9 recorded right ventricular pulse contours showed a diastolic dip.

The values observed during catheterization of normal subjects in this laboratory have been used as normal standards.

DISCUSSION

It has been our experience that limited or localized fibrosis of the myocardium produces no signs or symptoms; therefore such fibrosis presumably leads to no major hemodynamic abnormalities. Widespread fibrosis, however, does lead to hemodynamic changes and to signs and symptoms based upon them.[1] It appears that the hemodynamic effects of myocardial fibrosis depend on the nature, location, and extent of the fibrosis.

The general pattern of hemodynamic changes in this group of patients is consistent. This consistency stems partially from the fact that this series is a selected group in the sense that at some time in the study of each patient the possibility of constrictive pericarditis was considered.

* Three patients showed a pulmonary "capillary" pressure higher than pulmonary artery diastolic pressure. This technical error is related to the difficulty of obtaining accurate wedge pressures in critically ill patients.

The data presented indicate that the cardiac failure of myocardial fibrosis is a form of low-output failure. As a working hypothesis it is suggested that this low-output failure results from 2 basic physiologic defects, namely, limitation of diastolic filling and impairment of systolic emptying of the heart.

There is impressive evidence of limited diastolic filling. Extensive infiltration with dense fibrous tissue produces a stiffened and restricted myocardium that imposes its own altered characteristics of distensibility on both sides of the heart. This fibrous infiltration is evident by gross and microscopic examination and limited diastolic filling is manifest in the pressure plateau. The absence of a pressure plateau in some patients is not incompatible with this thesis. It appears probable that a pressure plateau is produced by myocardial fibrosis of such distribution that it limits diastolic filling to a similar degree on both sides of the heart. Isaacs et al.[8] studied the pathologic physiology of experimentally produced constrictive pericarditis and showed that interference with ventricular diastolic filling was a fundamental defect in this disease. This defect was explained as due to alterations of ventricular volume-elasticity characteristics by the pericardial scar. Production of isolated *left* ventricular pericardial constriction was followed by pulmonary congestion, as demonstrated by both physical signs and physiologic measurements. Isolated *right* ventricular pericardial constriction produced a striking increase in peripheral venous pressure, right atrial pressure, and right ventricular end-diastolic pressure. This took place without a concomitant rise in right ventricular systolic pressure, pulmonary artery pressure, or pulmonary "capillary" pressure. Constriction of *both* ventricles led to a pressure plateau by producing equivalent increases in all vascular pressures from the peripheral veins to the pulmonary "capillaries."

When myocardial fibrosis is predominantly left-sided there are relatively high pressures in the right ventricle (systolic), pulmonary artery, and pulmonary "capillaries." In such patients the absence of a plateau may be expected.

Further evidence of impairment of diastolic filling is supplied by pressure tracings. Those

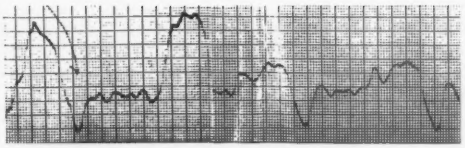


FIG. 3. Right ventricular and right atrial pressure tracings in a patient (R.C.) with myocardial fibrosis showing the "diastolic dip" and the "atrial M."

from the right ventricle may show a "diastolic dip" and those from the right atrium may show an "atrial M." These types of curves were originally described as occurring in constrictive pericarditis. An example of these pressure contours is shown in figure 3. In the ventricular curve, after the maximum pressure during systole, the curve falls rapidly but does not reach zero. Having reached its minimum, it rises steeply to a level between maximum and minimum and forms a plateau that does not change further until the onset of systole. The "atrial M" is characterized by a higher maximum than the normal, and by 2 plateau-like maxima of about equal height.

Most workers agree that such pressure contours indicate interference with diastolic filling.[9] When such curves are due to constrictive pericarditis, removal of the constricting pericardium and improvement in diastolic filling is associated with disappearance of the "diastolic dip" and the "atrial M."[10]

So much for the limitation of diastolic filling in patients with myocardial fibrosis. It is now pertinent to discuss the possibility of impairment of systolic emptying in these patients. It is difficult to devise a direct method of measuring impairment of systolic emptying and to rule out the effect of inadequate filling on systolic contraction. It seems reasonable to think that a myocardium, the muscle fibers of which are largely replaced by fibrous tissue, suffers impairment of contractility. It does not appear possible, for example, that the myocardial fibers shown in figure 4 (patients W. L. and N. L.), could contract effectively even if the stretch of the fibers were normal, but no quantitative evidence is available. Impairment of systolic emptying thus remains unconfirmed, but ap-

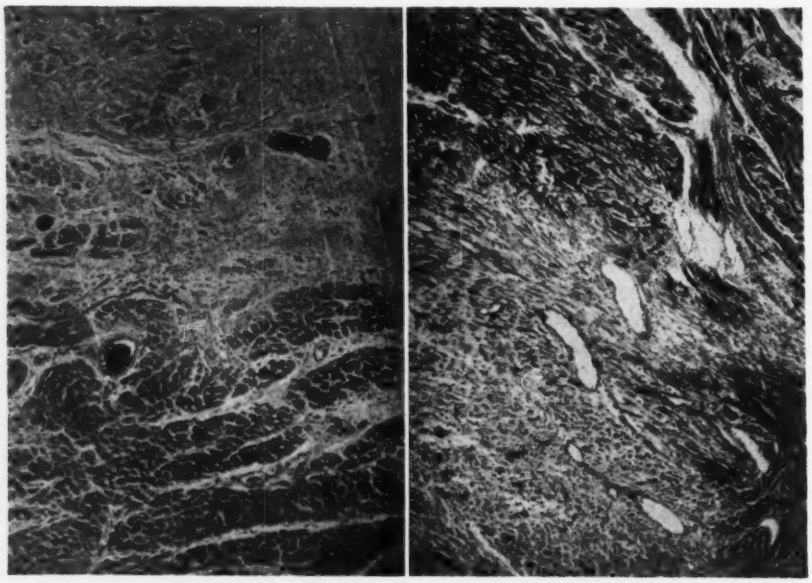


FIG. 4. Microscopic sections of myocardium in 2 patients (*left*, W. L.: *right*, N. L.) with myocardial fibrosis.

pears a probable part of the hemodynamic abnormalities of myocardial fibrosis.

The similarity of the hemodynamic changes in myocardial fibrosis and constrictive pericarditis is striking. A low cardiac output, elevated pressures from peripheral veins to pulmonary "capillaries," a pressure plateau, a "diastolic dip," and an "atrial M" are all findings generally present in both diseases. This similarity in manifestation stems from the fact that the 2 disorders cause similar changes in cardiac dynamics. Both lead to a somewhat rigid envelope of fibrous tissue that mechanically interferes with cardiac filling.

It is apparently not important that in the case of constrictive pericarditis this rigid area is located on the outside of the heart, while in the case of myocardial fibrosis it is situated within the myocardium. Indeed, endocardial fibroelastosis, a disease in which a rigid layer of fibrous tissue invades the inner layer of the heart, has been reported by Clark, Valentine, and Blount[11] to produce hemodynamic changes identical with those described above.

Since it has been shown that all 3 disorders, constrictive pericarditis, myocardial fibrosis, and endocardial fibroelastosis, have similar physiologic defects, it is not surprising that they present clinical pictures that are remarkably similar.[1, 2]

It is important to ask whether the patients reported here are really representative of the wide spectrum of patients with myocardial fibrosis. Hansen, Eskildsen, and Götzsche[10] have reported a single case of myocardial fibrosis with findings similar to those described above. Hetzel, Wood, and Burchell[12] have reported the results of cardiac catheterization in one patient with amyloid disease and in another with idiopathic heart failure. In each case the catheterization findings were similar to those reported in the present paper. Therefore, this group of patients does appear to be representative of patients with diffuse myocardial disease.

SUMMARY

The hemodynamic findings in 11 patients with diffuse myocardial fibrosis are described. Myocardial fibrosis can lead to low-output failure. The low output results from interference with diastolic filling and probably also

from interference with systolic emptying of the heart. The interference with diastolic filling is related to changes in the volume-elasticity characteristics of the fibrotic myocardium. Two other disorders—constrictive pericarditis and endocardial fibroelastosis—that have similar physiologic defects, show hemodynamic changes and a clinical picture similar to those of myocardial fibrosis.

Summario in Interlingua

Es describite le constatationes hemodynamic in 11 patientes con diffuse fibrosis myocardial. Iste condition pote resultar in disfallimento per basse grados de rendimento cardiac. Le basse rendimento es le consequentia de obstructiones del replenamento diastolic e probabilemente etiam del evacuation systolic del corde. Le obstruction del replenamento diastolic es relationate a alterationes del characteristicas de volumine e elasticitate del myocardio fibrotic. Duo altere disordines—pericarditis constrictive e fibroelastosis endocardial—in que simile defectos physiologic es manifeste exhibi simile alterationes hemodynamic e un simile tableau clinic.

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Tetralogy of Fallot

Clinical and Hemodynamic Spectrum of Combined Pulmonary Stenosis and Ventricular Septal Defect

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The considerable body of clinical and physiologic data in patients with the tetralogy of Fallot that has been accumulated over the past 15 years now indicates that the original concept of the lesion as a single, fairly narrowly limited entity is no longer valid. The tetralogy can now be demonstrated to occupy a broad spectrum in the field of congenital cardiac anomalies, representing widely varying forms. While the entity has been termed a tetralogy, only 2 features, namely the pulmonary stenosis and the ventricular septal defect, are essential in the determination of the clinical and physiologic pattern that patients with this defect portray.

THE tetralogy of Fallot is a commonly occurring malformation that is perhaps the most familiar of all cyanotic congenital cardiovascular anomalies, and has occupied a salient position in the field of congenital heart disease. It was one of the first congenital cardiac lesions to be described in the pathologic literature with reports appearing in the seventeenth and eighteenth centuries.[1, 2] It was also one of the first to receive clinical definition, mainly as a result of Fallot's descriptions in the latter part of the nineteenth century,[3] and it was the first of the cyanotic congenital cardiac anomalies to prove amenable to surgical correction. The success of the Blalock-Taussig procedure was a major factor in initiating the present era of widespread interest in diagnosis and therapy of congenital heart disease.[4]

The recent period of extensive investigation of congenital heart disease has resulted in the accumulation of a considerable body of clinical and physiologic data in patients with the tetralogy. This evidence indicates that the original concept of the lesion as a single, fairly narrowly limited entity, is no longer valid. The tetralogy of Fallot can now be shown to occupy a broad spectrum in the field of congenital cardiac anomalies presenting in widely varying forms.

This wide range occupied by the tetralogy of Fallot is more complex than that of the other common congenital cardiac lesions owing to the combinations of the anatomic defects constituting this anomaly. The complexity can be simplified by identifying the dominant anatomic features of the anomaly. It is obvious that right ventricular hypertrophy, one of the classic components of the tetralogy, is a purely secondary phenomenon and can consequently be eliminated as a significant element.

The role played by dextroposition of the aortic root is more difficult to assess. It is the opinion of the authors that this element of the tetralogy is not a dominant factor in determining the hemodynamic pattern. The concept, that an aortic root overriding the right ventricle is often more of an apparent nature than an actual anatomic malposition, has received increasing support in recent years.

The infundibular stenosis and the ventricular septal defect thus remain as the essential elements determining the clinical and physiologic patterns in patients with the tetralogy of Fallot.

The present report consists of an effort to define the widely varying forms of the tetralogy on the basis of variation in the severity of these 2 elements. The categories formed by combinations of the 2 defects in varying grades of severity are described and patients studied at this center are presented as examples.

CLASSIFICATION

A classification of the tetralogy of Fallot is proposed based on the possible combinations

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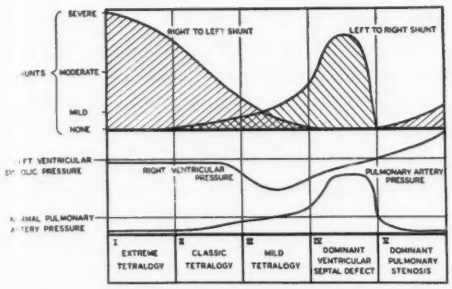

FIG. 1. A spectrum of the tetralogy of Fallot. The direction and the volume of shunting of blood through the ventricular septal defect are demonstrated schematically with the associated right ventricular and pulmonary artery pressures.

of infundibular stenosis of varying severity and a ventricular defect of varying size. A spectrum composed of these combinations is presented showing clinical and physiologic continuity within the group, yet permitting definition of recognizable subdivisions (fig. 1).

The first 3 groups of this spectrum represent 3 well-known forms of the tetralogy of Fallot, in which the 2 component lesions are of about equal but varying severity. The remaining 2 subdivisions constitute forms of the tetralogy in which one lesion is very severe and the other relatively mild, resulting in the hemodynamic pattern of the dominant defect (fig. 1).

Such a classification is of value in determining the optimal therapeutic course in patients with the tetralogy. Each of the subdivisions represents a separate category as regards the urgency, the value, and the technic of surgical therapy.

Type I: Extreme Tetralogy

The anatomic elements underlying this form of the anomaly consist of extreme pulmonary stenosis or complete atresia of the pulmonary artery associated with a large ventricular septal defect. The resulting hemodynamic characteristics include a large right-to-left shunt, a severely reduced or nonexistent pulmonary blood flow from the right ventricle, and equalization of pressures in the left and right ventricles. Clinically the typical features are cyanosis from birth, marked symptomatology, evidence of collateral circulation to the lungs, and frequently fatal termination in infancy or early childhood. Taussig has suggested the term "extreme tetralogy" to identify this lesion;[5, 6] "pseudotruncus arteriosus" is also used to designate this severe form, particularly when pulmonary atresia is present.

Excellent descriptions of this well-known variant of the classic tetralogy are present in the literature.[5, 6] Additional cases are therefore not presented. The hemodynamic aspects of the extreme tetralogy are similar to those of the classic tetralogy but reveal more marked peripheral arterial unsaturation. The arterial oxygen saturation levels are low at rest and are further reduced to astonishingly low levels on activity. Clinically the course of patients with the extreme tetralogy is marked by frequent episodes of paroxysmal hypoxia, which may be fatal, and severe limitation of exercise tolerance. Occasionally patients may develop extensive collateral circulation and live into adulthood. However, the usual course terminates in infancy or childhood. Auscultation reveals a systolic murmur along the left sternal border, which is considerably less intense than that accompanying the classic tetralogy, and on occasion no murmur is audible. The second heart sound at the base arises entirely from the closure of the aortic valve and at times, due to the relative position of the aorta, this second sound may be accentuated over the pulmonary area. A diagnostic auscultatory feature is a continuous cardiac murmur arising from the collateral circulation to the lungs.[5, 7] This murmur, produced by blood flow through bronchial and mediastinal arteries, is usually well heard over the back.

The electrocardiogram invariably demonstrates a pattern of right ventricular hypertrophy. The roentgenologic aspects of this lesion have been well described.[6, 8] The over-all heart size tends to be increased in contrast to the normal heart size usually present in the classic tetralogy. The collateral vessels produce a characteristic nodular hilar pattern and may indent the barium-filled esophagus.

The severe tetralogy may closely resemble tricuspid atresia in its clinical and radiologic aspects. The electrocardiogram is of considera-

ble importance in this differentiation as evidence of left ventricular dominance is usually present in the latter. A single ventricle with transposed great vessels and pulmonary stenosis produces a physiologic derangement similar to the severe tetralogy and may be difficult to differentiate. A true truncus arteriosus may also enter into the differential diagnosis should the pulmonary blood flow be greatly reduced.

A significant feature of the extreme tetralogy that segregates this lesion from the classic tetralogy is the unsatisfactory response to surgical measures. The hypoplasia of the main and at times of the right and left pulmonary arteries renders the establishment of a systemic anastomosis a very difficult or impossible technical procedure. Moreover, exploration of the hilar areas in search of a suitable vessel for anastomosis frequently results in destruction of the naturally occurring collateral vessels on which the life of these patients is dependent. Direct procedures relieving the pulmonary stenosis are of little benefit, since the pulmonary artery itself is decreased in size or atretic. Taussig and Bauersfield[5] reported a 26 per cent mortality in 27 patients considered to represent an extreme tetralogy. Operation was uniformly fatal in all 4 patients with pulmonary atresia described by Allanby and associates.[7]

Type II: Classic Tetralogy

The anatomic constituents of the classic tetralogy may be defined as severe pulmonary stenosis and a large ventricular defect. The hemodynamic changes resulting from the combination are a large right-to-left shunt and a small left-to-right shunt may also be present.[9-11] The pulmonary blood flow is decreased with a lowered pulmonary artery pressure.

The physiologic abnormalities occurring in the classic tetralogy are well described in the reports by various authors.[9, 11, 12] The pattern described conforms with the features outlined above.

The clinical characteristics of patients with this typical tetralogy have been lucidly presented by Taussig.[6] Early cyanosis, squatting, and episodes of paroxysmal dyspnea constitute an almost diagnostic triad. The physical examination reveals cyanosis and the features accompanying cyanosis, such as clubbing, hypertrophied gums, a "geographic" tongue, and injection of the conjunctivae. Auscultation reveals a systolic murmur at the left sternal border that may vary considerably in location and intensity from one patient to the next. A grade IV, harsh systolic murmur in the left third intercostal space might be considered the most common finding. The second heart sound in the pulmonary area probably arises from the aortic valve closure and may be normal or increased in intensity and is pure in quality.

Clinically patients with the classic form of tetralogy show cyanosis beginning early in childhood, a fairly severe limitation of exercise tolerance, and if untreated usually do not survive beyond childhood or adolescence.

The electrocardiogram demonstrates right ventricular hypertrophy.

Radiologic examination reveals a decreased vascularity of the lung fields, small and quiet right and left pulmonary arteries, and an absent or inconspicuous main pulmonary artery. The over-all heart size is characteristically within normal limits. However, the configuration of the heart reveals the classic "coeur en sabot" silhouette and indicates hypertrophy of the right ventricle. An additional characteristic radiologic feature is the occurrence of a right aortic arch. This abnormality occurs in approximately one fourth of patients with the tetralogy of Fallot. The angiocardiographic studies of Kjellberg and associates[12] have demonstrated clearly the dynamic radiographic features of the tetralogy. This classic form of the tetralogy has been well described over a period of many years. Case reports are therefore not included at this time.

Operative therapy can be said to be indicated in all patients with the classic tetralogy of Fallot. However, at the present time the decision as to the type of surgical therapy and the time at which such therapy should be instituted is difficult. Five years ago the management of these patients was relatively simple. An arterial anastomosis was the only form of therapy and was established either by the Blalock-Taussig method or by the Potts' technic. Marked symptomatic relief and un-

questionable prolongation of life have been achieved in many patients by this palliative procedure. However, development of the technic of pulmonary valvulotomy or infundibulectomy has now reached the stage where the mortality rate and the degree of symptomatic improvement is equal to or may exceed that of the shunt procedures. Since the relief of pulmonary stenosis is a curative rather than a purely palliative approach, it has been recommended by some authors as the method of choice.[13] At times, however, when the relief of the infundibular stenosis has been complete, or nearly so, an abrupt change in the hemodynamics may occur. Thus a significant left-to-right shunt has been noted with the development of rapidly increasing heart size and congestive failure.[14] The most recent phase of surgical therapy in the tetralogy consists of the complete correction of both the pulmonary stenosis and the ventricular defect. This ideal, totally corrective form of therapy is still accompanied by a rather high operative mortality. A conservative course at the present time might be to defer surgery whenever possible, pending further improvement in the truly corrective technics and to carry out a shunting procedure only on those patients whose clinical course permits no delay.

Type III: Mild Tetralogy

The third suggested subdivision of the spectrum of the tetralogy of Fallot is composed of acyanotic patients with minimal symptoms. The anatomic elements defining this type consist of pulmonary stenosis of a mild or moderate degree accompanying a ventricular septal defect of small or moderate size. This combination of anatomic features frequently results in an evenly balanced pattern with one defect governing the hemodynamic effects of the other. Shunting of blood through the ventricular defect due to its size is limited to relatively small volumes in either a right-to-left or left-to-right direction. The right ventricular pressure may be equal to or less than the left ventricular pressure and the pulmonary arterial pressure may be normal (patients 3, 4, 7, 8) or slightly elevated (table 2, patients 5, 6). Examples of this lesion are found in the rapidly expanding recent literature describing an increased pulmonary blood flow in the presence of pulmonary stenosis and have been termed atypical tetralogy of Fallot. A further source of illustrative cases from the literature is found in the description of patients with the classical form of the tetralogy who have had surgical relief of the pulmonary stenosis. Obliteration of a right-to-left shunt and the appearance of a mild left-to-right shunt have been documented in such patients.[13-15]

Data from 7 patients are presented in tables 1 and 2 as additional examples of this form of the atypical tetralogy. Patients 3 through 8 represent naturally occurring forms of the anomaly, while patient 1 illustrates the development of a type III pattern following direct infundibular resection in a patient with the classical form of the tetralogy.

Patients in this group present a uniform pattern of mild symptomatology and absence of cyanosis. The physical examination reveals a loud systolic murmur with a palpable thrill along the left sternal border in all patients. The area of maximum intensity of this murmur varied from the second to the fourth left intercostal space at the sternal border. A short middiastolic murmur was audible at the apex in 2 patients. The second heart sound in the pulmonary area was variable in intensity and degree of reduplication. The electrocardiogram revealed a similarly inconsistent pattern, as it varied from an essentially normal tracing in 1 patient, to right ventricular hypertrophy in 1 patient, and combined right and left ventricular hypertrophy in at least 1 patient (fig. 2, table 1). Fluoroscopic features of patients in this group also varied widely. The vascularity of the lung fields varied from normal to slightly increased. The size and the amplitude of pulsation of the main and of the right and left pulmonary arteries also varied. The heart size was enlarged in all but 2 patients (table 1).

At cardiac catheterization the pressures in the right side of the heart varied considerably in this group of patients; in 3 patients the right ventricular pressure was equal to the left ventricular pressure and in the other 3 patients the right ventricular pressure was definitely lower than in the left ventricle (table 2).

TABLE 1.—*Clinical Data in Eleven Patients with Various Forms of the Tetralogy of Fallot*

Class	Case number	Age and sex	Impairment of exercise tolerance	Physical examination					EKG		Radiology						
				Cyanosis	Thrill	Systolic murmur	Apical diastolic murmur	P_2	RVH	LVH	Peripheral vascularity of lung fields	RPA and LPA	MPA	Over-all cardiac enlargement	RVH	LVH	Aortic arch
2	1 preop.	8 M	Mild	Minimal	Absent	Grade 3 in 2nd l.i.s.	Absent	Normal Pure	Suggestive	Absent	Decreased	Normal size Quiet	Small	Absent	Present	Absent	Left
3	1 post-op.	8 M	None	Absent	Present	Grade 4 in 2nd l.i.s.	Absent	Normal Pure	Suggestive	Absent	Normal	Normal size Normal pulsations	Small	Slight	Present	Absent	Left
2	2 preop.	26 F	Moderate	Definite	Absent	Grade 3 in 2nd l.i.s.	Absent	Normal Pure	Present	Absent	Decreased	Normal size Quiet	Small	Absent	Present	Absent	Left
4	2 post-op.	26 F	Initially severe, later moderate	Definite	Present	Grade 4 in 2nd l.i.s.	Absent	Decreased	Present	Absent	Increased	Increased in size and pulsations	Increased in size and pulsations	Moderate	Present	Present	Left
	3	3 F	Mild	Absent	Present	Grade 5 in 2nd l.i.s.	Absent	Decreased	Present	Suggestive	Increased	Increased in size and pulsations	Increased in size and pulsations	Slight	Present	Slight	Left
3	4	6 F	None	Absent	Present	Grade 4 in 4th l.i.s.	Absent	Normal Split	RBBB	Present	Increased	Increased in size and pulsations	Increased in size and pulsations	Moderate	Present	Present	Left
3	5	8 F	None	Absent	Present	Grade 6 in 2nd l.i.s.	Present	Increased Pure	Present	Present	Increased	Increased in size and pulsations	Increased in size and pulsations	Moderate	Present	Present	Left
3	6	11 F	Mild	Absent	Present	Grade 5 in 2nd l.i.s.	Absent	Decreased Pure	Present	Suggestive	Increased	Increased in size and pulsations	Normal	Moderate	Present	Present	Left
3	7	4 F	None	Absent	Present	Grade 4 in 4th l.i.s.	Absent	Decreased Pure	Present	Absent	Normal	Small and Quiet	Increased	Normal	Present	Absent	Left
3	8	7 F	None	Absent	Present	Grade 5 in 3rd l.i.s.	Present	Normal Split	Absent	Absent	Increased	Increased in size Normal pulsations	Normal	Normal	Absent	Absent	Left
4	9	14 F	None	Absent	Present	Grade 4 in 4th l.i.s.	Absent	Decreased Pure	Absent	Absent	Increased	Normal in size and pulsations	Normal in size and pulsations	Moderate	Absent	Present	Left
4	10	4 M	Moderate	Absent	Present	Grade 4 in 3rd l.i.s.	Present	Loud Split	Present	Present	Increased	Increased in size and pulsations	Increased in size and pulsations	Moderate	Present	Present	Right
5	11	20 F	Moderate	Absent	Present	Grade 4 in 2nd l.i.s.	Absent	Decreased	Present	Absent	Decreased	Small	Small	Moderate	Present	Absent	Right

TABLE 2.—*Hemodynamic Data in Eleven Patients with Various Forms of the Tetralogy of Fallot*

Class	Case number	Age and sex	Pressures in mm. Hg						Blood oxygen saturation in % (average of multiple samples)					Pulmonary flow (L./min.)	Left-to-right shunt (L./min.)	Ratio left-to-right shunt/pulmonary flow	Systemic flow (L./min.)	Right-to-left shunt (L./min.)	Ratio right-to-left shunt/systemic flow	Surface area in $M.^2$
			RA	RV	Infundibulum	PA	PA wedged	SA	Venae cavae	RA	RV	PA	SA							
2	1 preop.	8 M	7/3	96/3	no evidence	15/8		100/80	66.2	68.6	66.6	63.4	82.5	3.0	0	0	5.3	2.3	43%	0.83
3	1 postop.	8 M	8/6	93/4		23/10		100/74*	66.9	68.4	80.4	78.0	94.5	5.3	2.1	40%	3.2	0	0	0.83
2	2 preop.	26 F	10/5	103/7	no evidence	18/8	9	111/69	58.3	60.1	59.4	60.5	81.3	3.2	0.5	16%	4.4	1.8	40%	1.87
4	2 postop.	26 F	17/6	90/20	questionable	50/32	20	114/52	58.6	55.8	78.2	78.5	89.3	9.1	5	55%	4.9	0	0	1.87
3	3	3 F	7/5	90/3	33/3	23/11		92/70	60.1	60.4	74.7	69.0	84.2	2.6	0.7	27%	2.8	0.9	32%	0.42
3	4	6 F	2/0	50/3	34/3	25/12	4	93/73	75.5	71.8	82.6	84.1	88.8	12.2	5.4	44%	10.0	3.1	31%	0.90
3	5	8 F	13/4	96/8	59/13	58/25	13	96/65	66.4	58.1	77.9	78.1	89.2	5.1	2.1	40%	3.7	0	0	0.87
3	6	11 F	10/0	108/5	38/6	39/20	8	115/80	69.9	69.5	81.9	76.6	92.7	6.7	2.9	43%	4.2	0	0	1.11
3	7	4 F	7/3	47/10	29/10	26/17		114/86	60.2	66.5	67.4	72.2	87.8	5.4	1.1	20%	5.8	1.5	25%	0.75
3	8	7 F	4/1	64/1	24/1	23/15		110/70	66.2	68.6	80.4	81.5	99.5	5.3	2.6	50%	2.6	0	0	0.86
4	9	14 F	7/3	57/8	35/8	33/13		156/70	73.8	69.4	83.8	84.0	94.0	13.7	6.6	48%	7.5	0	0	1.69
4	10	4 M	16/4	89/7	68/6	55/21	14	98/62	67.4	60.0	84.1	85.1	89.5	10.7	7.4	65%	4.0	0	0	0.63
5	11	20 F	17/4	220/10	76/10	13/8	6	120/76*	57.3	56.2	55.4	56.0	91.6	3.2	0	0	3.2	0	0	1.56

* Aortic pressure.

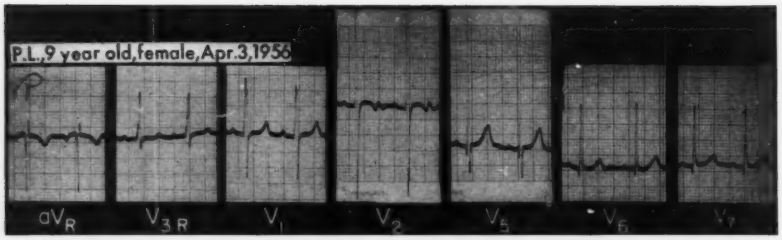

FIG. 2. Electrocardiogram in a patient with a mild form of the tetralogy of Fallot, patient 5. This tracing has been interpreted as demonstrating combined right and left ventricular hypertrophy.

Surgical intervention at this time in patients belonging to this group is seriously questioned, as removal of the pulmonary stenosis may eliminate the governing influence on the left-to-right shunt and thereby acutely create a great increase in the volume of the pulmonary blood flow that may result in dilatation and failure of the heart.

It is probably wise to postpone surgery for patients belonging to this category as long as possible and to wait until such time that the operative risk of combined closure of the ventricular septal defect and infundibulectomy is more acceptable.

Type IV: Dominant Ventricular Septal Defect

This variant is defined by the presence of mild infundibular stenosis with a large ventricular septal defect. Physiologically it is characterized by a large left-to-right shunt at the ventricular level with an increased pulmonary blood flow. The pressure in the right ventricle is usually equal to the left ventricular pressure, but may be lower. The infundibular stenosis, although mild, varies in degree as does the volume of the pulmonary blood flow, consequently the pressure gradient across the valve is of varying magnitude. The pressure in the pulmonary artery may be normal, but will usually be elevated. As the shunting of blood is from left to right, the peripheral arterial oxygen saturation is normal.

The salient clinical features of this atypical form of the tetralogy are the absence of cyanosis, symptoms of slight to moderately decreased exercise tolerance with increase in heart size and increased vascularity of the lung fields, and right and left ventricular hypertrophy.

This form of the tetralogy is less common and less well documented in the literature than the previous types. The 4 children described by Rowe and associates[16] are considered as representative examples of this variant of the tetralogy. Two of the patients described by Broadbent and associates,[17] with pulmonary blood flows of 12 and 12.9 L., might also be included in this category.

Two patients, 9 and 10, presented at this time, are considered to fall in this category, one of whom will be described in detail (tables 1 and 2).

Patient 10 was a well developed, acyanotic, active, 4-year-old boy who was initially thought to have a large ventricular septal defect with pulmonary hypertension. Later it was noted that the boy had a right aortic arch, and then the diagnosis was changed to a tetralogy of Fallot with a left-to-right shunt. The roentgenogram of the heart is presented in figure 3. Catheterization revealed a considerable left-to-right shunt with an increment in oxygen content of 2.6 volumes per cent in the right ventricle; the pressure in the right ventricle was 89/7 mm. Hg, while the pressure in the pulmonary artery was 55/21 mm. Hg. The pressure tracing (fig. 4) obtained on withdrawal of the catheter from the pulmonary artery to the right ventricle suggested the presence of an infundibular chamber.

At operation a mild infundibular stenosis was noted with a small infundibular chamber. The ostium infundibulum was estimated at the time of surgery to be 10 mm. in diameter. This was removed at surgery and a ventricular septal defect was also closed. The operation was without event, however the patient suddenly died 6 hours postoperatively. At post-

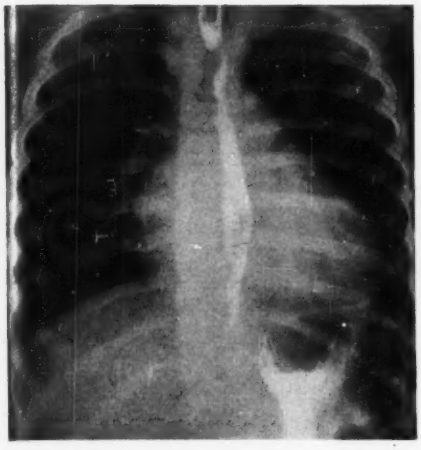

FIG. 3. Roentgenogram of patient 10, with a dominant ventricular septal defect and a right aortic arch.

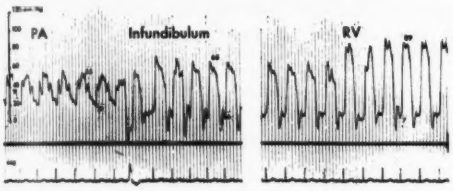

FIG. 4. Pressure record of patient 10, with a dominant ventricular septal defect, obtained on withdrawal of the catheter from the pulmonary artery into the right ventricle. The intermediate pressure zone is suggestive of the presence of an infundibular chamber.

mortem examination the ventricular septal defect was found to be completely closed and to measure 18 mm. in diameter. The infundibular chamber was 16 mm. in depth. The pulmonary valve was not stenotic, but was abnormal, as there were only 2 cusps present, 1 large cusp that occupied about two thirds of the valvular ring, and 1 smaller cusp that occupied the remainder of the ring. The aortic arch was on the right side (figs. 5 and 6).

The classical form of tetralogy may be transformed into the type of tetralogy under discussion at this time when the infundibular stenosis is largely removed without closure of the ventricular septal defect. Two such patients demonstrating this transformation have been previously reported.[14] They developed a sudden and excessive increase in pulmonary blood flow following removal of the obstruction in the right ventricular outflow tract. Physiologic studies obtained before and after operation in 1 of these patients clearly document a large left-to-right shunt at the ventricular level postoperatively.

An additional patient, no. 2, in whom infundibular resection was performed, was a well developed 26-year-old woman who was markedly cyanotic and moderately restricted in her activities. She was operated upon, and under hypothermia and circulatory occlusion the infundibular stenosis was resected adequately. Postoperatively her color greatly improved; however, she developed exertional dyspnea, orthopnea, and dependent edema. She was digitalized and placed on full therapy for congestive failure, which responded and cleared over a period of 3 months. At the present time, although her heart has increased in size, she no longer requires medication. There is no evidence of cyanosis and her exercise tolerance has markedly increased over her preoperative status.

Thus these patients demonstrate the inability of the left ventricle to compensate for the acute load that develops with the creation of a large left-to-right shunt. Similar postoperative excessive left-to-right shunts were mentioned by Sell and associates.[18] Thus depending upon the extent of the removal of the infundibular stenosis in patients operated upon by the direct infundibular approach the patient may be transformed into a mild tetralogy or the type of tetralogy under discussion at this time.

The problem of relative pulmonary stenosis must arise at this time. Experience with atrial septal defects associated with large pulmonary flows has revealed that considerable systolic pressure gradient may be present between the right ventricle and pulmonary artery in the absence of anatomic pulmonary stenosis. It is reasonable to assume that this phenomenon may also occur in patients with a ventricular septal defect and an increased pulmonary blood flow. However, studies of isolated ventricular defects have not shown functional pressure gradients comparable to those occurring in atrial septal defects.[19] The possibility of functional stenosis might arise in patient 10, in

FIG. 5 *Left.* Pathologic specimen of heart of patient 10. The left ventricle is opened and the (surgically closed) ventricular septal defect is visible beneath the aortic valve.

FIG. 6 *Right.* Pathologic specimen of patient 10. The right ventricle is opened. The infundibular chamber, and the (surgically closed) ventricular septal defect are seen beneath the bicuspid pulmonary valve.

whom the systolic pressure in the pulmonary artery was 55 mm. Hg and in the right ventricle 89 mm. Hg. However, the withdrawal pressure tracing from the pulmonary artery to the right ventricle suggested an infundibular chamber, and such a chamber was found at the time of operation and postmortem examination, as previously described.

The previously mentioned accessory diagnostic features of the tetralogy are also helpful in the differential diagnosis. A right aortic arch, which was present in patient 10, and in 1 of Rowe's patients,[16] is significant. Only rarely is a right aortic arch noted in patients with an isolated ventricular septal defect.

This group again offers evidence indicating the minor role played by an "overriding" aorta. In the autopsied patient of Rowe the overriding of the aorta was described as "considerable" and "little different from the classic case of the malformation." In patient 10, the aorta also appeared to override the defect and yet the shunting occurred exclusively in a left-to-right direction; in addition, there was no problem whatsoever in closing this defect at the time of operation.

Relative to surgery, patients with this type of the tetralogy are to be evaluated as patients with an isolated ventricular septal defect. Thus, if they have shown a large left-to-right shunt, an enlarged heart, and relatively low pulmonary vascular resistance, closure of the defect might be considered. The removal of the mild infundibular stenosis is of secondary importance and creates a minor additional problem if surgery is undertaken. However, inasmuch as the mortality and morbidity stemming from closure of the ventricular septal defect is still quite high, a conservative approach is recommended for the time being.

Type V: Dominant Pulmonary Stenosis

This variation consists of a combination of severe right ventricular outflow obstruction and a small ventricular septal defect. The systolic pressure in the right ventricle may greatly exceed that in the left ventricle. The consequent right-to-left shunt, however, is limited in magnitude by the size of the defect. This is an uncommon form of the tetralogy and little information is available in the literature regarding its characteristics. Clinically these patients are often considered to have valvular pulmonary stenosis with an intact ventricular septum. Patient 11 is an example of this form and will therefore be discussed in detail.

Patient 11 was a 20-year-old white girl. A heart murmur was heard at the time of birth. She had led a relatively normal life; however, she had experienced slight to moderate shortness of breath and fatigue on prolonged exertion for as long as she could remember. She had noted an increase in shortness of breath and fatigue with episodes of mild ankle edema during the past year, and at the time of examination she could walk only a few blocks at a slow pace, and could not climb a flight of stairs without having to stop because of dyspnea and fatigue.

Physical examination revealed an alert, well developed young lady. No cyanosis or clubbing was present. Distinct a-waves were noted in the deep neck veins. There was a slight precordial bulge and precordial activity was diffuse. The apex beat was just outside the left midclavicular line, and a right ventricular lift was felt beneath and just to the left of the lower sternum. Palpation also revealed a systolic thrill along the upper left sternal border that was maximum in the second left intercostal space. A grade IV, harsh systolic murmur was heard along the left sternal border, also maximum in the second left intercostal space, but loud in the third and fourth interspaces, and louder in the third than in the first. The second heart sound in the left second intercostal space was decreased in intensity.

Fluoroscopy revealed the pulmonary vascularity to be at the lower limits of normal. The main pulmonary artery was not prominent. The heart was moderately enlarged with prominence of the right ventricle and right atrium. The aortic arch was on the right and the aorta also descended on the right (fig. 7).

The electrocardiogram revealed evidence of severe right ventricular hypertrophy and right atrial enlargement (fig. 8).

The patient had been referred with the diagnosis of isolated valvular pulmonary stenosis. However, because of the right aortic arch, and the location of the murmur, it was thought that she had an atypical form of the tetralogy of Fallot. This latter diagnosis was confirmed by the information obtained at cardiac catheterization (table 2). The oxygen saturation of the peripheral arterial blood was within normal limits for this altitude, thus indicating that there was no significant right-to-left shunting of blood, and there was no evidence of a left-to-right shunt. The catheter was passed from the right ventricle through a ventricular septal defect into the aorta. The right ventricular pressure was 220/10 mm. Hg, while the pressure in the aorta was 120/76 mm. Hg. The pressure in the pulmonary artery was only 12/8 mm. Hg. The pressure record on withdrawal of the catheter from the pulmonary artery to the right ventricle suggested an infundibular

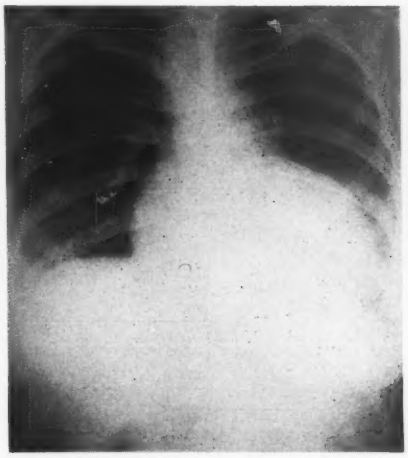

FIG. 7. Roentgenogram of patient 11, with a dominant infundibular stenosis and a right aortic arch.

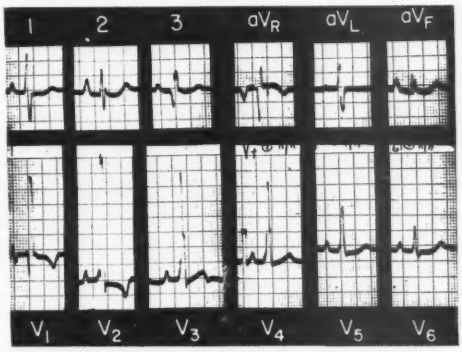

FIG. 8. Electrocardiogram of patient 11, with dominant infundibular stenosis. This tracing has been interpreted as demonstrating right ventricular hypertrophy.

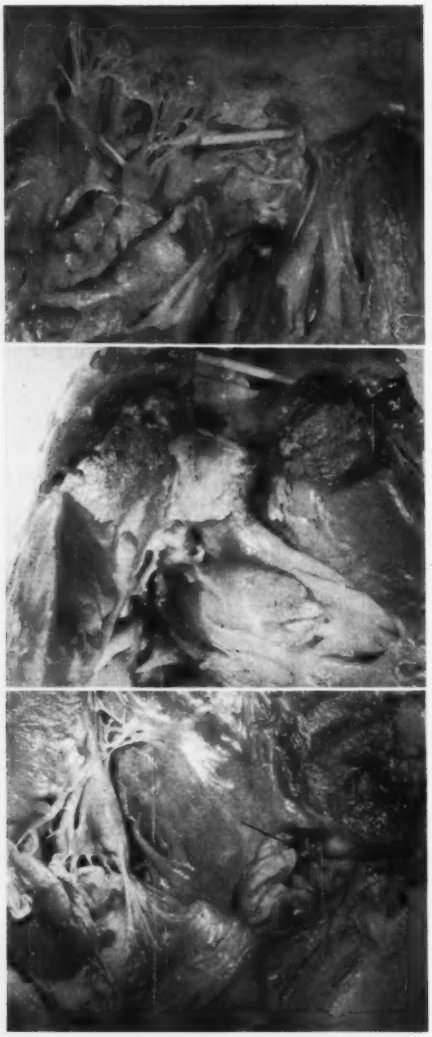

FIG. 9 *Top*. Pathologic specimen of patient 11. A wooden probe is passed through the small ventricular septal defect which is covered by a tricuspid leaflet.

FIG. 10 *Middle*. Pathologic specimen of patient 11. The infundibular chamber is opened and the narrow fibrous ostium infundibulum (which has been removed partially at surgery) is seen.

FIG. 11 *Bottom*. Pathologic specimen of patient 11. The ventricular septal defect (indicated by arrow) is seen beneath the aortic valve.

chamber. The right atrial pressure was 17/4 mm. Hg, giant a-waves being present.

Infundibulectomy was performed without event, but complications developed postoperatively and the patient died on the third postoperative day. At postmortem examination the findings were as expected. There was a small, short infundibular chamber with a fibrous ring forming a very narrow ostium infundibulum, which had been partially excised at surgery. The ventricular septal defect was very small, being but 5 mm. in diameter, and in addition the tricuspid valve leaflet was positioned in such a manner that it tended to close the defect. The right ventricle was markedly hypertrophied, being 18 mm. in thickness (figs. 9, 10, and 11).

A similar patient was demonstrated by Goetzsche and associates[11] with a figure showing a "drawback" from aorta to the right ventricle with a higher systolic pressure in the right ventricle than in the aorta. A possibly similar case is a patient of Brock and Campbell[13] in whom an excessively high right ventricular pressure was recorded.

This type lesion thus masquerades as an isolated pulmonary stenosis, either valvular or infundibular. It is quite probable that many patients diagnosed as isolated infundibular stenosis may actually not have an intact ventricular septum, but have a small, physiologically insignificant defect in the septum.

The surgical approach to patients with this lesion should be directed at complete removal of the infundibular stenosis. The ventricular septal defect is small and thus one would not be concerned with the development of a significant left-to-right shunt, should the pulmonary stenosis be completely removed.

SUMMARY

The tetralogy of Fallot is the most common cyanotic congenital cardiac defect that is compatible with the maintenance of life beyond infancy and early childhood. It was the first cyanotic congenital lesion amenable to the furtherance of life expectancy by operative intervention. Interest in this lesion was also the main stimulus for the development of our present fund of knowledge relative to congenital cardiac defects.

However, because of this early experience with the classic tetralogy and the so-called "blue baby operation," we have in general come to consider that the patient with tetralogy

of Fallot must be cyanotic and markedly incapacitated. Otherwise, the diagnosis of tetralogy of Fallot is not seriously entertained.

The considerable body of clinical and physiologic data in patients with the tetralogy that has been accumulated over the past 15 years now indicates that the original concept of the lesion as a single, fairly narrowly limited entity is no longer valid. The tetralogy of Fallot can now be demonstrated to occupy a broad spectrum in the field of congenital cardiac anomalies, presenting in widely varying forms. While the entity has been termed a tetralogy, it is becoming apparent that only 2 features, namely, the pulmonary stenosis and the ventricular septal defect, are essential in the determination of the clinical and physiologic patterns of this defect.

Thus, certainly the right ventricular hypertrophy, one of the classic components of the tetralogy, is a purely secondary phenomenon and can be dismissed as a significant factor in the determination of the clinical picture. The role of dextroposition of the aortic root is more difficult to assess and possibly not so easily dismissed. However, clinical and physiologic evidence together with the findings at operation in these patients suggests that the dextroposition of the aorta is of functional origin and not anatomic.

This idea was first noted by Eisenmenger in his discussion of ventricular septal defect in 1898,[20] when he pointed out that in the presence of large ventricular septal defects, the anatomic relationship of the aorta to the membranous portion of the septum is such that overriding may occur, even though the aorta arises in an entirely normal position from the left ventricle. Thus, in the tetralogy of Fallot, if the ventricular septal defect is closed, there usually is no technical difficulty relative to the position of the aorta.

It is the size of the ventricular defect and the degree of the pulmonary stenosis and the varying combinations of severity of these 2 defects that are responsible for the clinical and physiologic findings. The classical tetralogy has a moderately sized ventricular septal defect and a moderate to severe pulmonary stenosis, resulting in relatively equal pressures in the 2 ventricles, a decreased pulmonary blood flow, and a predominantly right-to-left shunt. However, the patient with the tetralogy of Fallot may be acyanotic, relatively asymptomatic, and masquerade as a patient with an isolated pulmonary stenosis. The pulmonary stenosis is marked and the ventricular septal defect small, resulting in a pressure within the right ventricle greatly exceeding that within the left ventricle. There will be a minimal right-to-left shunt and no left-to-right shunt.

The other end of the spectrum also reveals an acyanotic patient with almost full activity. This patient has a large ventricular septal defect and a very mild infundibular stenosis with a resulting large left-to-right shunt and no right-to-left shunt. The pressure in the right ventricle may be equal to or less than that within the left ventricle. Pulmonary hypertension may exist and the systolic pressure gradient between the pulmonary artery and right ventricle may be minimal. This patient is usually thought to have a large ventricular septal defect, and the diagnosis of tetralogy of Fallot is not considered.

Should we continue the use of the term tetralogy of Fallot? Probably for a better understanding of the clinical and hemodynamic features of this anomaly, this term should be discarded. However, it is certain that it will disappear from our terminology only slowly and with great reluctance.

Summario in Interlingua

Le tetralogia de Fallot es le plus commun congenite defecto cardiac cyanotic ancora compatibile con le mantenentia del vita in ultra del prime infantia. Illo esseva le prime congenite lesion cyanotic in que il esseva possibile meliorar le probabilitate del superviventia per interventiones chirurgic. Le interesse de iste lesion esseva etiam le principal stimulo in le disveloppamento de nostre currente fundo de cognoscentias relative a congenite defectos cardiac.

Tamen, a causa de iste experientias initial in casos del classic tetralogia de Fallot e a causa del si-appellate operation pro "babies blau," nos tende a opinar in general que le patiente con tetralogia de Fallot debe esser cyanotic e marcatemente incapacitate. In casos que non corresponde a iste conception, le diagnose de

tetralogia de Fallot non es seriemente prendite in consideration.

In le curso del passate 12 annos un massa considerabile de datos clinic e physiologic in re patientes con tetralogia de Fallot ha essite accumulate, e le resultato es que nos debe concluder que le conception original de iste lesion como un sol e satis strictemente circumscripte entitate ha perdite su validitate. Il es nunc possibile demonstrar que le tetralogia de Fallot occupa un large spectro in le campo del congenite anomalias cardiac e que illo se presenta sub le guisa de multiple variationes. Ben que le entitate ha essite designate como tetralogia, il deveni de plus in plus apparente que solmente 2 tractos—i.e. stenosis pulmonar e defecto ventriculo-septal—es essential in le determination del configuration clinic e physiologic de iste defecto.

Assi, hypertrophia dextero-ventricular—un del componentes classic del tetralogia—es certo un phenomeno purmente secundari e pote esser rejicite como factor significative in le determination del tableau clinic. Le rolo de dextroposition del radice aortic es plus difficile a evalutar e possibilemente non pote esser rejicite con le mesme grado de assecurantia. Tamen, observationes clinic e physiologic insimul con constatationes al operation de iste patientes pare indicar que le dextroposition del aorta es de origine functional e non anatomic.

Iste notion esseva primo signalate per Eisenmenger in su discussion del defecto ventriculo-septal in 1898,[20] quando ille observava que in le presentia de grande defectos ventriculo-septal le relation anatomic inter le aorta e le portion membranose del septo es de natura a render possibile le occurrentia de un cavalcamento, ben que le sito del origine del aorta ab le ventriculo sinistre es totalmente normal. Per consequente, si in casos de tetralogia de Fallot le defecto ventriculo-septal es claudite, il ha usualmente nulle difficultate technic quanto al position del aorta.

Il es le magnitude del defecto ventricular e le grado del stenosis pulmonar e le multiple combinationes del varie grados de severitate de iste 2 defectos que es responsabile pro le constatationes clinic e physiologic. Le forma classic de tetralogia de Fallot ha un defecto ventriculo-septal de magnitude moderate e un stenosis pulmonar de grado moderate o sever con le resultato de relativemente equal pressiones in le 2 ventriculos, un reducite fluxo de sanguine pulmonar, e un derivation predominantemente dextero-sinistre. Tamen, patientes con tetralogia de Fallot pote esser acyanotic e relativemente asymptomatic, e lor comportamento pote similar le comportamento de patientes con isolate stenosis pulmonar. In tal casos le stenosis pulmonar es marcate e le defecto ventriculo-septal parve, con le resultato que le pression intra le ventriculo dextere excede grandemente le pression intra le ventriculo sinistre. Le derivation dextero-sinistre es minimal, e nulle derivation sinistro-dextere es presente.

Etiam le altere extremo del spectro monstra un patiente acyanotic con quasi non-restringite activitate. Iste patiente ha un grande defecto ventriculo-septal e un levissime stenosis infundibular con le resultato de un pronunciate derivation sinistro-dextere e nulle derivation dextero-sinistre. Le pression in le ventriculo dextere pote esser equal o inferior al pression in le ventriculo sinistre. Hypertension pulmonar pote exister, e le gradiente de pression systolic inter le arteria pulmonar e le ventriculo dextere pote esser minimal. In casos de iste typo, on conclude usualmente que le patiente ha un grande defecto ventriculo-septal, e le diagnose de tetralogia de Fallot non es prendite in consideration.

Il es probabile que abandonar le termino tetralogia de Fallot promoverea le appreciation del characteristicas clinic e hemodynamic de iste anomalia, sed il es a expectar que su disparition ab nostre terminologia va esser lente e ardue.

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Medical Eponyms

By ROBERT W. BUCK, M.D.

Fick Principle. Professor Adolf Fick (1829–1901) of Würzburg discussed "The Measurement of the Amount of Blood in the Ventricles" (*Ueber die Messung des Blutquantums in den Herzventrikeln*) on July 9, 1870 before the Physicomedical Society of Würzburg. An abstract of his discussion appears in the *Verhandlungen der Physikal.-medicin. Gesellschaft in Würzburg.* 2 (neue Folge): *Sitzungsberichte für 1870*, pp. xvi–xvii, Würzburg, 1872.

"The amount of oxygen taken from the air by an animal during a given time is measured as well as the amount of carbon dioxide given off. During the experimental period, a sample of arterial and one of venous blood is also taken. The oxygen content and carbon dioxide content is measured in both. The difference between the two oxygen measurements reveals how much oxygen each cubic centimeter of blood has taken up in its passage through the lungs, and thus we know the total amount of oxygen taken up during a definite period of time. Consequently the number of cubic centimeters of blood which passed through the lungs during this time may be reckoned, or if we divide by the number of heart beats during this period of time, we may determine how many cubic centimeters of blood were put out with each cardiac systole."

Quantitative Analysis of the Electrocardiographic Pattern of Hypopotassemia

By Borys Surawicz, M.D., Harold A. Braun, M.D., William B. Crum, M.D., Robert L. Kemp, M.D., Seymour Wagner, M.D., and Samuel Bellet, M.D.

Electrocardiographic patterns typical of hypopotassemia and compatible with hypopotassemia were defined on the basis of the number of electrocardiographic signs of hypopotassemia present in 2 leads (generally leads II and V_3). In 50 hypopotassemic patients a good correlation was found between the electrocardiographic pattern and plasma potassium concentration. Appearance of the electrocardiographic signs of hypopotassemia was not prevented by disturbance of other plasma electrolytes or by blood pH.

ELECTROCARDIOGRAMS of patients with low concentrations of extracellular potassium frequently show characteristic abnormalities that disappear after administration of potassium salts.[1, 2] Regression of the electrocardiographic pattern of hypopotassemia during administration of potassium is characterized by a gradual increase of T-wave amplitude, decrease of U-wave amplitude, and diminution of S-T segment depression in the standard limb and precordial leads without any change in Q-T or other components of the Q-U interval.[1] This sequence of regression suggests that the converse, the evolution of the hypopotassemia pattern, consists of a progressive decrease of T-wave amplitude, increase of U-wave amplitude, and S-T segment depression in the standard limb and precordial leads. Accordingly, a schematic construction of 5 patterns, representing 5 stages in the evolution of the electrocardiogram in hypopotassemia, has been made.[1] At that time no attempt was made to analyze the electrocardiographic signs of hypopotassemia in a quantitative manner or to correlate these signs with the concentrations of extracellular potassium.

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This work was aided by a grant from the Eli Lilly Company of Indianapolis, Indiana, and by a grant from the National Institutes of Health, grant 141(C6); and was done during Dr. Surawicz's tenure of a Research Fellowship of the American Heart Association and while Drs. Braun and Crum were trainees, National Heart Institute, National Institutes of Health.

During the past few years we have gained an impression that in a majority of patients with hypopotassemia, electrocardiograms can be correlated with the concentration of extracellular potassium. However, since others[3-7] have failed to find a correlation between the electrocardiogram and serum potassium level, it was thought that a new investigation might be helpful. We made an attempt to develop quantitative criteria for objective evaluation of the electrocardiographic changes in these patients. We also considered certain factors other than the potassium concentration that may influence the electrocardiogram of patients with hypopotassemia.

This paper presents the results of the correlation between the electrocardiogram and plasma potassium level in 50 patients with hypopotassemia.

Methods and Material

Fifty adult patients with plasma potassium levels below 3.5 mEq./L. were selected for the study. Description of patients whose electrocardiograms we studied is presented in a separate communication,[8] which also contains the methods and results of the plasma electrolyte studies. Patients were subdivided into 3 groups on the basis of plasma potassium concentration: group A consisted of 17 patients whose plasma potassium concentrations were between 2.0 and 2.7 mEq./L., group B of 13 patients with concentrations from 2.71 to 2.98 mEq./L., and group C of 20 patients with concentrations from 3.0 to 3.49 mEq./L.

Twelve-lead electrocardiograms were recorded in each instance immediately after the blood was drawn for determination of plasma electrolytes. Potassium chloride infusion was then begun. Potassium was administered at a rate of 8 ml. per minute

in a concentration of 60 mEq./L. of 0.45 per cent saline. In 5 patients for whom sodium chloride was contraindicated, potassium was given as a solution of 60 mEq./L. of distilled water. The average dose of 34 mEq. (range 21 to 60 mEq.) was given in an average time of 71 minutes (range 45 to 120 minutes). During intravenous administration of potassium chloride, electrocardiograms were recorded at intervals of 2 to 5 minutes. In each case electrocardiograms were also frequently recorded during the subsequent hospital course.

Methods of measurement of the intervals from the onset of QRS to the apex of T wave (Q-aT), the end of T wave (Q-T), and the apex of the U wave (Q-aU) have been described previously.[9, 10] Methods of differentiating between T wave and U wave in doubtful cases have been described elsewhere.[1, 11]

Results

Correlation with Plasma Potassium Concentration. After a careful inspection of all electrocardiographic tracings, it was found that an analysis of 2 leads of each electrocardiogram was sufficient for the purpose of this study. One limb lead and 1 precordial lead, the lead with the greatest U-wave amplitude, were chosen for analysis. The limb lead of choice was usually lead II, but occasionally lead III or aV_F. The precordial lead of choice was usually lead V_3, but occasionally lead V_2 or V_4. This choice was based on previous observations that the largest U wave in hypopotassemia usually is present in leads V_2 and V_3, while the possibility of both the U-wave and T-wave patterns of hypopotassemia being registered in the same lead is greater in the limb leads.[1]

Detailed analysis of 50 electrocardiograms was carried out with regard to the following 3 signs: amplitude of the U wave exceeding 1 mm.; amplitude of the U wave exceeding the amplitude of the T wave in the same lead;* and depression of the S-T segment of 0.5 mm. or more. These 3 signs will be designated as positive signs of hypopotassemia. Since an analysis of 2 leads was made in each instance, a given electrocardiogram could contain a maximum of 6 positive signs. All electrocardiograms were grouped with regard to the number of positive signs of hypopotassemia that they contained. Representative electrocardiograms in each category are illustrated in figures 1 to 7.

The 2-lead electrocardiograms of each patient were submitted for inspection to several experienced observers who were asked to separate the tracings into 3 groups: electrocardiograms *typical* of hypopotassemia, *compatible* with hypopotassemia, and *nondiagnostic* of hypopotassemia. It was found that electrocardiograms designated as *typical* of hypopotassemia usually showed at least 3 positive signs, while the electrocardiograms designated as *compatible* usually showed 1 or 2 positive signs. Thus, we defined a tracing *typical* of hypopotassemia as an electrocardiogram containing 3 or more positive signs in the 2 analyzed leads. A tracing was defined as *compatible* with hypopotassemia if the electrocardiogram contained any 2 positive signs or only 1 positive sign related to the U wave. *Nondiagnostic* tracings showed either no positive signs of hypopotassemia or only a depression of the S-T segment in 1 of the 2 leads. Typical electrocardiograms were most commonly encountered in group A, less commonly in group B, and seldom in group C (fig. 8). The only 4 electrocardiograms with 6 positive signs occurred in group A. Electrocardiograms designated as compatible with hypopotassemia and the nondiagnostic electrocardiograms were most commonly encountered in groups B and C. Thus, in group A with the lowest potassium levels, 13 patients (78 per cent) had typical, 2 patients (11 per cent) compatible, and 2 patients (11 per cent) nondiagnostic electrocardiograms. In group C with the highest plasma potassium level, 2 patients (10 per cent) had typical, 9 patients (45 per cent) compatible, and 9 patients (45 per cent) nondiagnostic electrocardiograms.

Correlation with Plasma Concentration of Electrolytes and with Blood pH. The average plasma potassium concentration was lowest in

* We were aware that in certain cases of advanced hypopotassemia the amplitude of the deep negative T wave could exceed the amplitude of the U wave. In such cases an absence of the reversal of U/T ratio would be wrongly interpreted as absence of a positive sign of hypopotassemia. However, no such cases were encountered in this study. In the presence of diphasic negative-positive T waves only the amplitude of the positive component was taken for measurement.

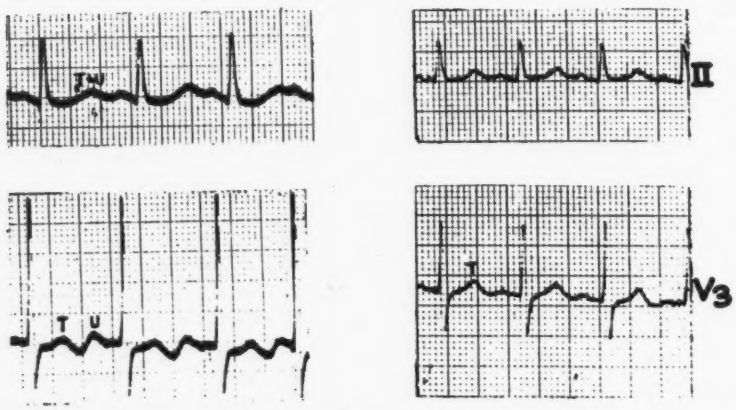

FIG. 1. Electrocardiogram typical of hypopotassemia with 6 positive signs. *Left*. A tracing of a patient with hepatic coma and long-standing vomiting and diarrhea. Plasma K^+ 2.2, Na^+ 133, Ca^{++} 4.15, Cl^- 87 mEq/L., pH 7.38. Note the depression of the S-T segment in both leads. Further note that the T wave and U wave are completely merged in lead II, but the U wave can be identified as a separate wave following a diphasic T wave in lead V_3. Amplitude of the U wave exceeds the amplitude of the T wave. Q-aT interval measures 0.24 second (expected Q-aT 0.28 second), Q-T interval measures 0.36 second (expected Q-T 0.36 second), Q-aU interval 0.46 second (expected Q-aU 0.45 second). *Right*. The electrocardiogram after 3 days of intravenous administration of potassium salts and blood transfusions. Note the normal appearance of the tracing.

patients with a typical electrocardiographic pattern (2.64 mEq./L.), higher in those with a compatible electrocardiogram (3.01 mEq./L.), and highest in patients with nondiagnostic tracings (3.22 mEq./L.). The average concentrations of sodium, chloride, calcium, and average blood pH were nearly identical in all 3 groups.

Modification of the Pattern by Other Electrocardiographic Abnormalities. In each of the patients an attempt was made to determine whether the electrocardiographic abnormalities observed in the presence of hypopotassemia were due to hypopotassemia alone or to some unrelated factors. In 44 patients the non-hypopotassemic electrocardiographic pattern was available for the comparison with the hypopotassemic pattern. In 27 patients the non-hypopotassemic electrocardiogram was normal, 10 showed left ventricular hypertrophy and "strain," 4 a varying degree of lowering and inversion of T wave and depression of the S-T segment, 2 "ischemic"-pointed and inverted T waves, and 1 a pattern of acute myocardial infarction.

Plasma potassium levels of patients with left ventricular hypertrophy and "strain" pattern who had electrocardiograms typical of or compatible with hypopotassemia were generally higher than plasma potassium levels of patients with a normal electrocardiographic pattern in the same groups. In 3 patients depression of the S-T segment and a low T wave in lead II, and in 2 patients a tall U wave in lead V_3 persisted after plasma potassium became normal. Thus, the presence of left ventricular hypertrophy and "strain" pattern may exaggerate certain features of the hypopotassemia pattern. Depression of the S-T segment and lowering or inversion of the T wave due to factors other than hypopotassemia also exaggerated the electrocardiographic pattern of hypopotassemia. This relation was suggested by the fact that the only 2 patients in group C who were considered to have the typical pattern of hypopotassemia showed S-T and T abnormalities with normal plasma potassium level after correction of potassium deficiency. In 1 of the 2 patients with deeply inverted pointed T waves presence of this abnormality appeared to obscure some of the typical signs of hypopotassemia. The same was also true of the elevation of the S-T segment in 1 case of acute myocardial infarction; here the presence of a high U-wave amplitude

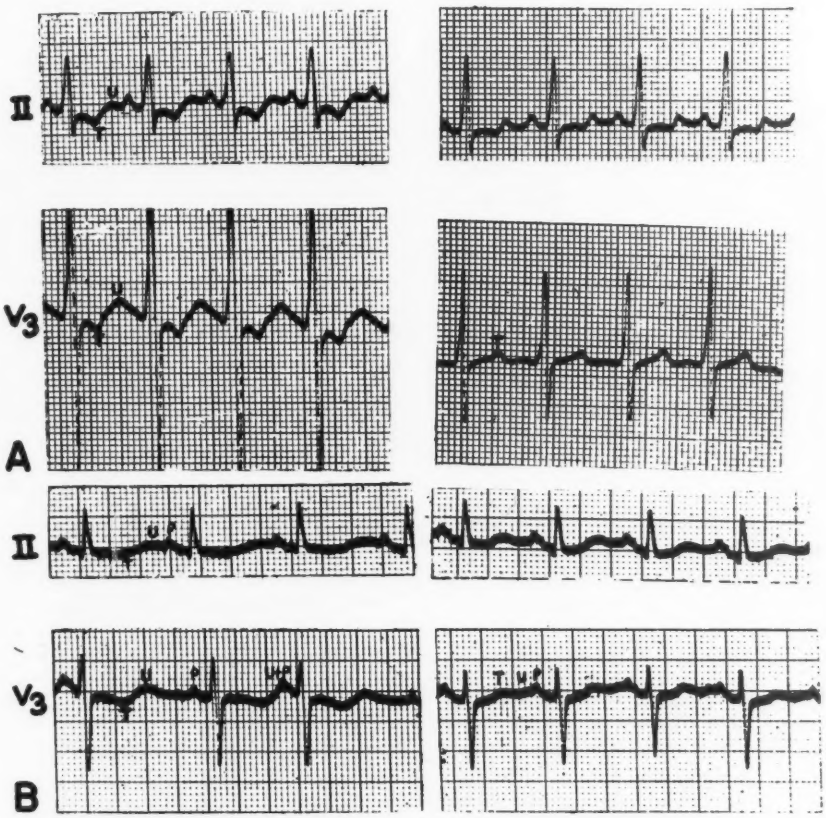

FIG. 2. Electrocardiograms typical of hypopotassemia with 5 positive signs. *A., Left.* An electrocardiogram of a hypertensive patient following treatment of diabetic acidosis with large amounts of insulin, saline, and glucose intravenously. Plasma K^+ 2.5, Na^+ 139, Ca^{++} 5.35, Cl^- 115, HCO_3^- 18 mEq./L., pH 7.30. Note the depression of the S-T segment and the tall U wave in both leads. The amplitude of the U wave exceeds the amplitude of the T wave in lead V_3. The negative T and the positive U are merged in lead II, but in lead V_3 there is a kink between the 2 waves. Q-aT interval measures 0.26 second (expected Q-aT 0.25 second), Q-T interval 0.29 second (expected Q-T 0.31 second), and Q-aU interval 0.38 second (expected Q-aU 0.40 second). *A., Right.* the electrocardiogram after administration of potassium salts and feeding. Plasma K^+ 5.2, Na^+ 136, Ca^{++} 4.3, Cl^- 92, HCO_3^- 25 mEq./L., pH 7.36. Note the disappearance of the U wave and of the depression of the S-T segment in lead V_3. *B., Left.* An electrocardiogram of a debilitated patient with a cerebrovascular accident and 3 weeks of anorexia. Plasma K^+ 2.5, Na^+ 141, Ca^{++} 5.1, Cl^- 92, HCO_3^- 33 mEq./L., pH 7.51. Note the depression of the S-T segment and the diphasic, poorly defined T wave merged with the U wave in both leads. The amplitude of the U wave in lead V_3 exceeds 1 mm. In lead II, the amplitude of the U wave is less than 1 mm. but is greater than the amplitude of the T wave. The third complex in lead V_3 is an atrial premature beat and a merging of the P wave and the U wave can be seen. The Q-aT and the Q-T interval could not be measured. The Q-aU interval measures 0.46 second (expected Q-aU 0.47 second). *B., Right.* The electrocardiogram after oral administration of potassium for 2 days. Plasma K^+ 3.2, Na^+ 149, Ca^{++} 4.85, Cl^- 97, HCO_3^- 29 mEq./L., pH 7.50. Note the increase of the T wave and the decrease of the U-wave amplitude.

permitted the classification of the electrocardiogram as compatible with hypopotassemia (fig. 5).

Modification of the Pattern by Different Heart Rates. The electrocardiographic patterns typical of or compatible with hypopotassemia occur less commonly when the heart rate is rapid. Thus, the only nondiagnostic electrocardiograms in groups A and B appeared in patients with rapid heart rates. On the other hand, the only electrocardiograms typical of or compatible with hypopotassemia in group C occurred in the group of patients with the slowest heart rate. Electrocardiograms typical of hypopotassemia occurred in patients with R-R intervals between 0.61 and 0.88 second in

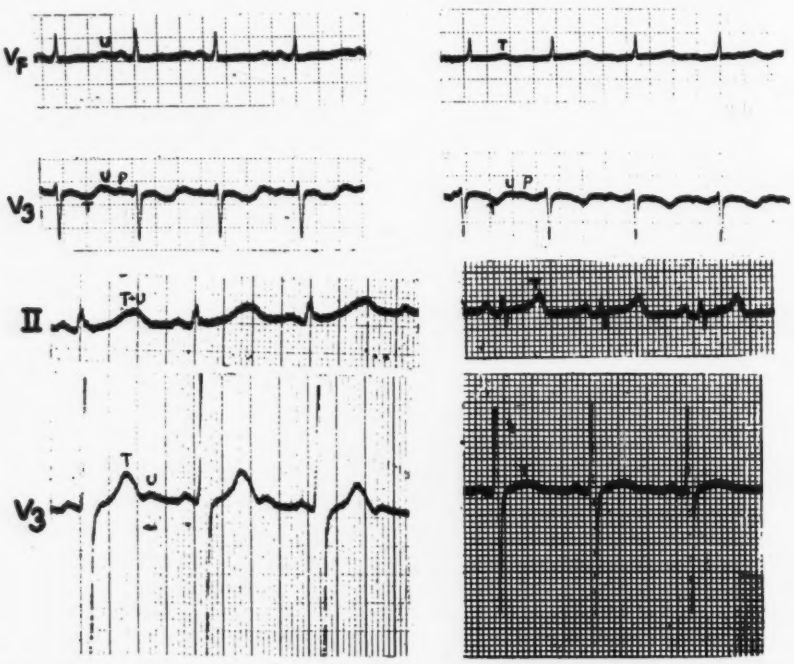

FIG. 3 *Top*. Electrocardiogram typical of hypopotassemia with 4 positive signs. *Left*. An electrocardiogram of a patient with liver cirrhosis and long-standing vomiting. Plasma K^+ 2.5, Na^+ 143, Cl^- 102, HCO_3^- 20 mEq./L., pH 7.41. Note the depression of the S-T segment in lead V_3. Further note that the T wave is poorly defined and partly merged with the U wave. The amplitude of the U wave exceeds the amplitude of the T wave in both leads and the U wave exceeds 1 mm. in lead V_3. The Q-aT and Q-T intervals could not be measured. The Q-aU interval measures 0.44 second (expected Q-aU 0.43 second). *Right*. The electrocardiogram 15 minutes after potassium infusion was discontinued. Plasma K^+ 3.0, Na^+ 142, Ca^{++} 4.15, Cl^- 107, HCO_3^- 16 mEq./L., pH 7.38. Note the more positive and the less inverted T waves in lead V_F and V_3 and the decreased amplitude of the U wave. The Q-aT interval measures 0.35 second (expected Q-aT 0.27 second), Q-T interval 0.41 second (expected Q-T 0.36 second) and Q-aU 0.44 second (expected Q-aU 0.45 second).

FIG. 4 *Bottom*. Electrocardiogram typical of hypopotassemia with 3 positive signs. *Left*. An electrocardiogram of an alcoholic patient with a history of long-standing vomiting. Plasma K^+ 2.4, Na^+ 123, Cl^- 63 mEq./L., pH 7.60. Note the merging of the T wave with the U wave in lead II; in some cycles a small notch could be seen between the 2 waves. The amplitude of the U wave in lead II appears to exceed the amplitude of the T wave. The U wave in lead V_3 is tall but clearly separated from the T wave. The Q-aT interval measures 0.31 second (expected Q-aT 0.30 second), the Q-T interval 0.42 second (expected Q-T 0.38 second), and the Q-aU interval 0.47 second (expected Q-aU 0.48 second). *Right*. The electrocardiogram after 5 days of intravenous and oral potassium administration. Plasma K^+ 5.1, Na^+ 125, Ca^{++} 4.3, Cl^- 91 mEq./L., pH 7.40. Note the changes of the T and U waves.

group C, with R-R intervals of 0.51 to 0.88 in group B, and with R-R intervals of 0.38 to 0.88 second in group A. These results were interpreted as evidence that the recognition of the electrocardiographic pattern of hypopotassemia becomes progressively more difficult with increasing heart rate. The difficulty in recognition of hypopotassemia when the heart rate is fast is due to several factors. One of these is the progressive decrease of the U-wave amplitude when the heart rate increases.[12] Another difficulty caused by tachycardia is the frequent merging of the U wave with the preceding T or the subsequent P wave.

We found that in several cases merging of the U wave with the P wave could be recognized as such when attention was directed to the shape of the P wave. A P wave that is merged with a positive U wave begins above the baseline and ends at the baseline. This gives the P

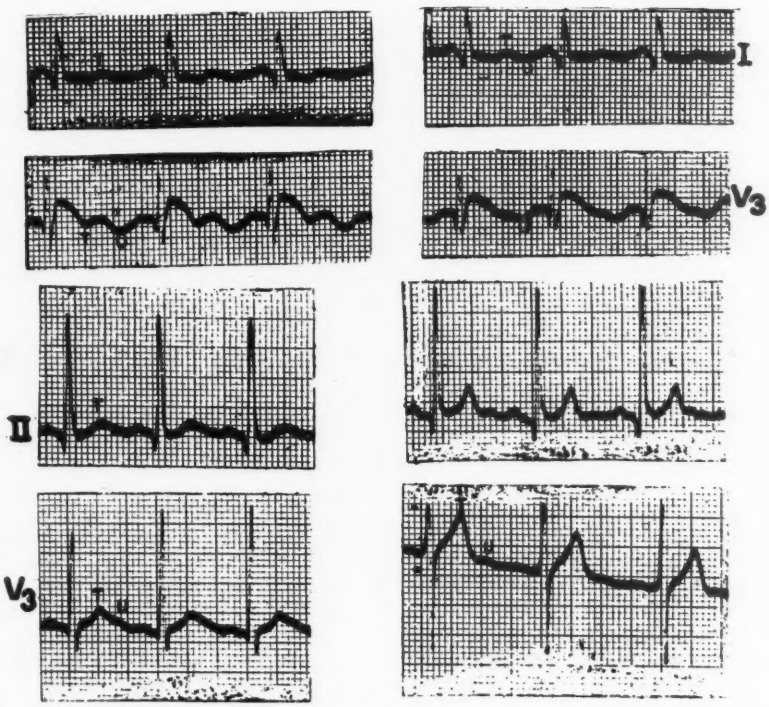

FIG. 5 *Top*. Electrocardiogram compatible with hypopotassemia with 2 positive signs. *Left*. An electrocardiogram of a patient with a history of prolonged vomiting and a recent myocardial infarction with shock. The tracing was recorded shortly after infusion with hypertonic saline. Plasma K^+ 2.8, Na^+ 171, Cl^- 148, HCO_3^- 36 mEq./L., pH 7.61. Note the Q wave in both leads and S-T segment elevation in lead V_3. The U wave in lead V_3 is deeply inverted and is of greater amplitude than the T wave. The Q-aT interval measures 0.28 second (expected Q-aT 0.29 second). The Q-aU interval measures 0.48 second (expected Q-aU 0.47 second). *Right*. The electrocardiogram after potassium infusion. Plasma K^+ 3.1 mEq./L. Note the decrease of the amplitude of the U wave.

FIG. 6 *Bottom*. Electrocardiogram compatible with hypopotassemia with 1 positive sign. *Left*. An electrocardiogram of a patient following perforation of a duodenal ulcer and gastrectomy. Plasma K^+ 2.9, Na^+ 133, Ca^{++} 4.25, Cl^- 93, HCO_3^- 28 mEq./L. Note the merging of the U wave with the T wave. The amplitude of the U wave in lead V_3 probably exceeds 1 mm. The Q-aT interval measures 0.21 second (expected Q-aT 0.22 second), Q-T interval 0.31 second (expected Q-T 0.30 second). *Right*. The electrocardiogram after 8 days of feeding. Plasma K^+ 4.6, Na^+ 146, Ca^{++} 4.6, Cl^- 92, HCO_3^- 23 mEq./L., pH 7.36. Note the increase of the amplitude of the T wave and the decrease of the amplitude of the U wave.

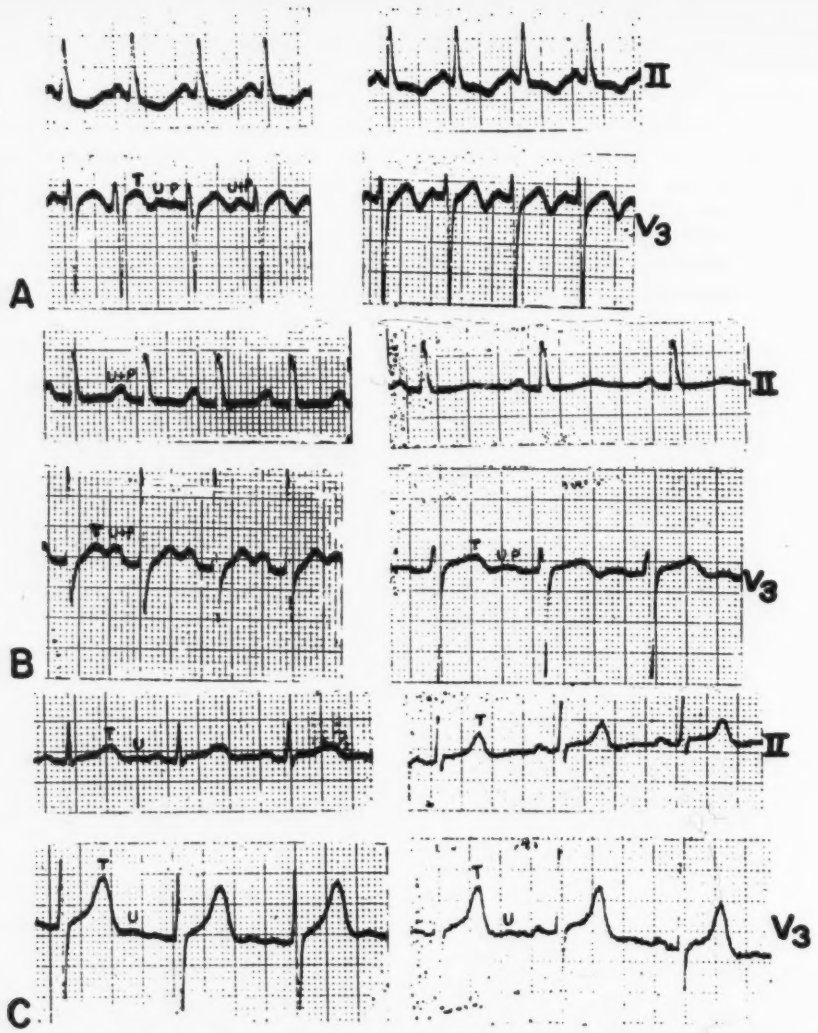

FIG. 7. Electrocardiograms nondiagnostic of hypopotassemia in patients with hypopotassemia. *A., Left.* An electrocardiogram of a patient with pseudobulbar palsy, inadequate diet, infusions of potassium-free solutions, and steroid therapy. Plasma K^+ 2.5, Na^+ 132, Cl^- 96, HCO_3^- 19 mEq./L., pH 7.54. Note the tachycardia and the absence of electrocardiographic signs of hypopotassemia. The P wave and the U wave are merged, simulating a high-amplitude P wave. The third complex in lead V_3 follows a premature beat and appears after a longer R-R interval. This demonstrates the separation of the U wave from the following P wave and shows the true amplitude of the P wave. *A., Right.* The electrocardiogram after potassium infusion. Plasma K^+ 3.3, Na^+ 137, Ca^{++} 3.6, Cl^- 96, HCO_3^- 17 mEq./L., pH 7.54. Note the decrease of the P wave amplitude, probably caused by a decrease of the U-wave amplitude. *B., Left.* An electrocardiogram of a patient in hepatic coma. Plasma K^+ 2.8, Na^+ 125, Ca^{++} 3.9, Cl^- 68 mEq./L. Note the absence of electrocardiographic signs of hypopotassemia. The P-R interval is prolonged and the P wave appears to be merged with the U wave, probably accounting for the high amplitude of the P wave. Note the tilted P wave in lead V_3 with the onset situated farther above the base line than the end of the P wave. *B., Right.* The electrocardiogram after 7 days of feeding and intravenous potassium administration. Plasma K^+ 4.5, Na^+ 141, Cl^- 77, Ca^{++} 4.9 mEq./L., pH 7.44. Note that the U wave and the P wave are still merged in lead V_3; the marked decrease in P-wave amplitude probably is due to the decreased amplitude of the U wave. *C., Left.* An electrocardiogram of a patient with cholelithiasis, vomiting, and diarrhea. Plasma K^+ 3.0, Na^+ 133, Ca^{++} 4.5, Cl^- 93 mEq./L., pH 7.37. Note the absence of electrocardiographic signs of hypopotassemia. *C., Right.* The electrocardiogram after 12 days of adequate diet. Plasma K^+ 4.2, Na^+ 141, Ca^{++} 4.65, Cl^- 93 mEq./L., pH 7.35. Note that the T waves have become more peaked in lead II.

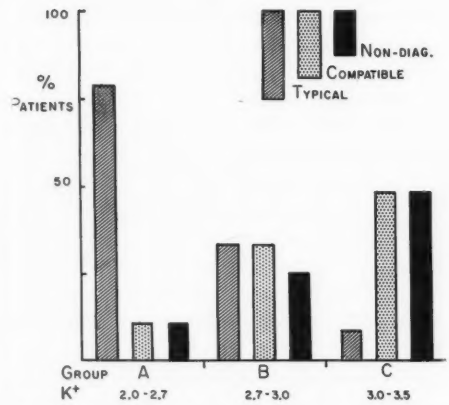

FIG. 8. Correlation between the number of positive electrocardiographic signs of hypopotassemia and the severity of hypopotassemia.

wave a characteristic tilted appearance and frequently contributes to a significant increase of the amplitude of the P wave (fig. 2*B* and 7*B*). We have recognized the usefulness of the sign of a "tilted P wave" in the diagnosis of hypopotassemia after repeatedly observing a progressing descent of the onset of the P wave during administration of potassium to patients with hypopotassemia. Figure 7*A* demonstrates the apparent increase of the amplitude of the P wave due to the merging of the latter with the U wave.

Correlation of Individual Positive Signs and Plasma Potassium Level. Correlations between S-T, T, and U-wave abnormalities and the plasma potassium were possible in the 27 patients whose electrocardiogram became normal when the plasma potassium rose to normal.

1. *S-T segment.* Depression of the S-T segment of 0.5 mm. or more was present in 9 of the 27 patients. The plasma potassium level in these 9 patients ranged from 2.0 to 2.83 mEq./L. The electrocardiograms of these patients were characterized by a poor definition of the T wave in the lead with the depressed S-T segment. The T wave was considered in all these cases as a diphasic, negative-positive wave, and the positive component was usually of low amplitude. The electrocardiographic patterns were considered as typical of hypopotassemia in 8 out of 9 patients with S-T depression. It was concluded that depression of the S-T segment caused by hypopotassemia is a sign of an advanced hypopotassemia.

2. *T wave.* The T wave was positive and its amplitude could be determined in the precordial lead in all 27 patients. In 12 patients the amplitude of the T wave was 1 mm. or less, in 8 patients it ranged from 1.5 to 3.0 mm., and in 7 from 4.0 to 8.5 mm. The group of patients with the highest T waves and the group of patients with the medium-sized T waves had similar plasma potassium concentrations (2.95 and 3.01 mEq./L.).

The group of patients with the lowest T waves had lower average (2.63 mEq./L.) and lower range of plasma potassium concentrations than the other 2 groups. It was concluded that there was no direct correlation between the amplitude of the T wave and plasma potassium level until the amplitude of the T wave fell below 1 mm. in the precordial lead with the highest U wave. However, T-wave amplitude below 1 mm. was usually found in patients with lowest plasma potassium levels and typical electrocardiographic patterns of hypopotassemia.

3. *Ratio of the U-wave amplitude to the T-wave amplitude.* The analysis was limited to the U/T ratio in the precordial lead. The U/T ratio was less than 0.5 in 8 patients, between 0.5 and 1.0 in 6 patients, and more than 1.0 in 9 patients. The groups of patients with the smallest and the medium ratios had similar plasma potassium concentrations (2.94 and 3.05 mEq./L.). The group with the highest U/T ratios had a lower range and a lower average (2.52 mEq./L.) potassium concentration than the other 2. All electrocardiograms in this group were considered to be typical of hypopotassemia. It was concluded that there was no direct correlation between plasma potassium level and U/T ratio in the precordial lead with the highest U wave until this ratio exceeded 1. However, the U/T ratio of more than 1 usually occurred in patients with lowest plasma potassium levels.

4. *Amplitude of the U wave.* There was no significant correlation between the amplitude of the U wave and plasma potassium concentration. The U-wave amplitude was found to be related to the heart rate.[12]

Duration of the Q-aT, Q-T, and Q-aU Interval. The present study afforded us an opportunity to check the validity of the results of previous study of this subject.[1] The details of measurements will not be repeated and only the essence of the results will be presented. Q-aT, Q-T, and Q-aU intervals in the electrocardiograms of 42 patients were measured and expressed as a percentage of the normal expected value.[10] Electrocardiograms of 8 patients with heart rates faster than 110 per minute were excluded because no normal values for such heart rates were available to us.

The Q-aU interval was within ±10 per cent of the expected value in 36 out of 42 patients, slightly prolonged (+16 and +17 per cent) in 2 patients, and not measurable in 4 patients.

The Q-aT and Q-T intervals will be discussed together. We subdivided the electrocardiograms of our patients into a group with normal and a group with prolonged Q-T or Q-aT intervals. The group with normal intervals (within 10 per cent of the expected value) included 18 patients with both intervals measurable before administration of potassium and 7 patients in whom one or both of these intervals became measurable only after administration of potassium. The group with prolonged intervals had Q-aT intervals ranging from +12 to +45 per cent and Q-T intervals from +12 to +33 per cent. The group consisted of 8 patients in whom the prolonged intervals were measurable before the administration of potassium and of 9 patients in whom the intervals became measurable only after administration of potassium.

Comparison of plasma potassium levels in both groups of patients demonstrated similar ranges (2.21 to 3.48 and 2.00 to 3.35 mEq./L.) and almost identical average values (2.87 and 2.84 mEq./L.). There was, however, a significant difference in plasma calcium concentration. The group with normal intervals had plasma calcium concentrations ranging from 3.7 to 6.6 mEq./L. with an average value of 4.76 mEq./L., while the group with prolonged intervals had plasma calcium concentrations ranging from 3.05 to 5.05 mEq./L. with an average value of 3.9 mEq./L. Plasma calcium concentrations below 4.5 mEq./L. were encountered in 7 out of 25 patients with normal intervals and in 14 out of 17 patients with prolonged intervals. In 2 of the 3 remaining patients with normal calcium concentration and prolonged intervals, there was electrocardiographic evidence of heart disease of the type often associated with Q-T prolongation.

It was concluded that prolongation of the Q-aT and Q-T intervals, defined according to previously described criteria,[9, 10] was related to hypocalcemia but not to hypopotassemia.

Effect of Intravenous Potassium Administration in 42 Patients. The amplitude of the P wave decreased in 7, increased in 1, and remained unchanged in the remaining patients. The duration of P-R interval shortened from 0.01 to 0.02 second in 3 patients and remained unchanged in all others. The QRS voltage decreased in 36 and remained unchanged in 6 patients. The amplitude of the T wave increased in 32, remained unchanged in 6, and decreased in 3 patients. The latter 3 patients had inverted T waves. The apex of T wave could not be defined in 13 out of 50 patients with hypopotassemia for one or more of the following reasons: isoelectric T wave, diphasic T wave in all leads, or T wave merged with the U wave. After potassium administration the apex of the T wave could be defined in all but 1 patient. The amplitude of the U wave remained unchanged in 4 and decreased in the remaining patients. The duration of the Q-aT, Q-T, and Q-aU intervals, corrected for sex and heart rate, remained essentially unchanged in all patients in whom measurements could be done before and after administration of potassium. The heart rate remained unchanged in 22, slightly decreased in 9, and slightly increased in 11 patients.

Ectopic beats were present in 13 patients with plasma potassium levels ranging from 2.0 to 3.35 mEq./L. There was no relation between the presence of ectopic beats and plasma potassium concentration. The ectopic beats were supraventricular in 9, ventricular in 3, and both supraventricular and ventricular in 1 patient. After intravenous administration of potassium chloride supraventricular ectopic beats disappeared in 5, decreased in 1, underwent no change in 3, and increased in 1 patient

The ventricular ectopic beats decreased in 2, underwent no change in 1, and increased in 1 patient. Special features of ectopic beats occurring in hypopotassemia are described in a separate study.[13]

Discussion

The electrocardiographic pattern of hypopotassemia can be defined with accuracy by the use of certain quantitative criteria. These are related to the U-wave amplitude, the relation between U and T amplitude, and to S-T segment displacement. Our preliminary observations indicate that this typical electrocardiographic pattern of hypopotassemia is fairly specific and that the only known clinical situation in which such an electrocardiographic pattern frequently appears in patients with normal plasma potassium is a combined effect of digitalis and quinidine.[1]

In our subjects there was a good correlation between the number of electrocardiographic signs of hypopotassemia and the plasma potassium concentration. Unless tachycardia is present, if the potassium concentration is below 2.7 mEq./L. a tracing typical of hypopotassemia is to be expected. All patients with plasma potassium concentrations exceeding 2.7 mEq./L. showed a wide variety of electrocardiographic patterns. The presence of such a wide variety of patterns can probably be explained by 2 factors. First, normal serum potassium concentration may range from 3.59–3.72 to 5.5–5.62 mEq./L.[14, 15] Therefore, a hypopotassemic serum level can be expected in some individuals after a very small and in others only after a considerable decrease in potassium concentration. Secondly, there is a wide range of normal T-wave amplitudes in different individuals.[16] When the T wave initially is small, a slight decrease in amplitude may cause a reversal in T/U ratio and contribute to a typical hypopotassemia pattern. A similar degree of lowering of an initially tall T will not greatly disturb the T/U ratio and may go unnoticed (fig. 7*C*). The normal T wave apparently was tall and peaked and the electrocardiogram showed no sign of hypopotassemia when the plasma potassium level was 3.0 mEq. L.

Our findings confirm the general experience that electrocardiographic changes diagnostic of hypopotassemia appear only with seriously low potassium levels,[17] and that T-wave lowering occurs regularly only with potassium levels below 3.0 mEq./L.[18] However, our observations are in contrast to those of other workers who describe a poor correlation between the electrocardiographic pattern and the severity of the hypopotassemia.[3-7] Two factors may account for this disagreement: the small number of patients with potassium concentration below 2.7 mEq./L. observed by these investigators, and the different methods of electrocardiographic evaluation.[1]

The cause of the electrocardiographic findings in hypopotassemia is uncertain. Dependence on the plasma potassium concentration is suggested by the rapidity of development of electrocardiographic abnormalities following perfusion of the isolated heart with potassium-free fluid.[19] and the acute removal of potassium by hemodialysis in dogs.[20] We have observed a similar rapidity during glucose infusions in normal subjects and in patients with diabetic acidosis.[21] However, it has been postulated that the electrocardiographic findings in hypopotassemia are due to a change in ratio of intracellular to extracellular potassium.[1, 22] If this is true, the results of our study may simply indicate that the change of ratio in the myocardium is determined largely by a change in the extracellular potassium concentration. This appears probable because of the large change in ratio produced by a small change in extracellular potassium concentration. For instance, a change of plasma potassium concentration from 4.0 to 2.0 mEq./L. corresponds to a decrease of 50 per cent. Such decreases in the content of cellular myocardial potassium have not been reported to our knowledge. It has been stressed that in cats subjected to various experimental procedures the changes in the myocardial concentration of potassium were smaller than changes in the skeletal muscle potassium, and the reported results show changes of myocardial potassium of less than 15 per cent.[23] Likewise, in rats subjected to experimental potassium depletion, a stability of the content of myocardial potassium has

been emphasized and compared with more variable concentrations of potassium in the skeletal muscle.[24] Furthermore, it has been shown that the intracellular potassium concentration in hearts perfused with solutions containing low, normal, and high potassium concentrations was not significantly different.[25] If these results of animal experiments are applicable to the human heart, one may assume that the potassium gradient across the myocardial cell membrane is largely determined by the extracellular potassium concentration.

Our findings indicate that abnormal concentrations of electrolytes other than potassium do not interfere with the identification of electrocardiographic signs of hypopotassemia. An exception may be encountered in patients with pronounced hypocalcemia; here the Q-T prolongation, due to hypocalcemia, causes a complete merging of the T wave with the U wave.[1, 26]

Alkalosis and acidosis did not prevent the appearance of typical electrocardiographic signs of hypopotassemia. A typical pattern in the presence of acidosis is illustrated in figure 2*A*, and has been found by others.[27-29] The effect of blood pH on intracellular myocardial potassium is not known, but in striated muscle intracellular potassium content was similar in patients with acidosis and alkalosis.[30] Abrams, Lewis, and Bellet[31] found that electrocardiographic changes occurring in acidotic and alkalotic dogs could be correlated with changes in extracellular potassium concentration.

Conflicting data are reported by Magida and Roberts,[32] who concluded that the electrocardiographic changes observed in dogs with hypopotassemia should be attributed to metabolic alkalosis per se. However, when their electrocardiographic illustrations are evaluated by the criteria presented in this paper, it is reasonable to conclude that the changes observed in hypopotassemic alkalotic dogs are indeed due to the hypopotassemia.*

Of the several features that may obscure the typical electrocardiographic signs of hypopotassemia, tachycardia was the most common in our patients. However, even when the R-R interval is short, the presence of a tall U wave frequently can be suspected when the P wave is abnormally tall and tilted, e.g., figures 1, 2, 6*b*, and 6*c* of reference 1 and figure 2 to 5 of reference 33. In these cases, similar to the cases presented in this study, administration of potassium caused an apparent lowering and leveling of the P wave. However, it must be stated that the tilted appearance of the P wave occurs not only when P is merged with U, but also when the P wave is merged with the T wave. Thus, we have observed tilted P waves in patients without hypopotassemia in several cases with a prolonged P-R interval, supraventricular premature beats, and some other situations in which the P wave was merged with the T wave.

In our experience a false electrocardiographic diagnosis of hypopotassemia has not been common. Depression of the S-T segment, when not accompanied by other electrocardiographic signs of hypopotassemia should not lead to a suspicion of this electrolyte disturbance. In agreement with other workers,[20] our findings indicate that S-T depression is a sign of advanced hypopotassemia, always accompanied by increase in U-wave amplitude. Tall U waves

* Magida and Roberts[32] pointed out that the electrocardiogram of the dog with alkalosis and hypopotassemia illustrated in their figure 1 bears similarity to the electrocardiogram of a dog with alkalosis and no hypopotassemia, illustrated in their figure 2, but no similarity to the electrocardiogram of a dog with hypopotassemia and no alkalosis, illustrated in their figure 3. An inspection of figures 1 to 3 of this paper permits a different interpretation of the illustrated electrocardiograms from that offered by the authors. The electrocardiogram of a dog with hypopotassemia and alkalosis in their figure 1 shows an elevated P wave that has an onset situated farther from the base line than the end, and thus is very similar to the tilted P wave observed by us in patients with hypopotassemia and tachycardia. The S-T segment is depressed and the T wave has a rounded appearance. The electrocardiogram of a dog with alkalosis but no hypopotassemia, in their figure 2, shows a smaller amplitude of the P wave, the P wave does not have the tilted appearance, the S-T segment is not depressed, and the T wave has not a rounded, but a peaked appearance when serum potassium is 5.0 mEq./L. Accordingly, we think that the illustrated electrocardiographic changes in dogs with hypopotassemia are caused by hypopotassemia and not by alkalosis.

may be present without hypopotassemia in patients with left ventricular hypertrophy and "strain" pattern. The combination of tall U waves and S-T depression in left ventricular hypertrophy and "strain" may lead to a suspicion of hypopotassemia. However, in our experience, when hypopotassemia complicates the left ventricular "strain" pattern, S-T depression was found, not only in the limb and left precordial leads, but also in leads V_{1-3}. Since an uncomplicated left ventricular hypertrophy and "strain" pattern usually shows an S-T elevation in the leads with tall T and U waves (leads V_{1-3}), the finding of S-T depression in these leads becomes a useful diagnostic sign of hypopotassemia.

We found no changes of configuration or amplitude of the P waves or QRS complexes that could be attributed to hypopotassemia. However, following the administration of potassium, there was a fairly constant decrease in QRS amplitude and a frequent decrease of P-wave amplitude.

Since excessive potassium is known to decrease the action potential of the myocardial fiber,[34] hypopotassemia might be expected to cause increased QRS and P amplitude. However, we have not considered the lowering of amplitude as a specific potassium effect because we have repeatedly observed a decrease of QRS and P wave amplitude similar to that occurring during infusion of potassium chloride also during infusion of saline.[35]

In our subjects, the incidence of arrhythmia was not correlated with the degree of hypopotassemia. However, many of our patients had, in addition to hypopotassemia, either heart disease or other conditions known to be associated with cardiac arrhythmias. Lepeschkin and Rosenbaum[36] suggested that increased U amplitude facilitates appearance of premature beats, analogous to the appearance of ectopic beats when a critical height of the afterpotential is reached. In their figure 2, appearance of ventricular irritability was associated with progressive increase in U-wave amplitude.

A similar experience was recorded by Stephens[37]: during treatment of diabetic acidosis with glucose and insulin, ventricular premature beats and bigeminy developed when the U waves became large.

Ventricular tachycardia or fibrillation has not been reported as a cause of death in patients with documented hypopotassemia, but such a possibility appears to exist.

Summary

In 50 hypopotassemic patients, 2 leads (generally leads II and V_3) of the electrocardiogram were analyzed with regard to the following electrocardiographic signs of hypopotassemia: (1) amplitude of the U wave greater than 1 mm., (2) a ratio greater than 1 of U-wave to T-wave amplitude in the lead with the tallest U wave, and (3) S-T segment depression more than 0.5 mm. Depending on the number of signs present in the 2 leads, electrocardiograms were termed *typical* of hypopotassemia (3 or more signs), *compatible* with hypopotassemia (2 signs, or only 1 sign related to the U wave), and *nondiagnostic* of hypopotassemia (no sign, or only S-T segment depression in 1 of the leads).

A correlation was found between the electrocardiographic pattern and the plasma potassium concentration. In 17 patients with a potassium level between 2.0 and 2.7 mEq./L., 78 per cent had electrocardiograms typical of hypopotassemia. In 20 patients with a plasma potassium between 3.0 and 3.49 mEq./L., 90 per cent of the tracings were either nondiagnostic of or merely compatible with hypopotassemia. In 4 subjects, 6 signs were present in the 2 electrocardiographic leads; each of these patients was in the group with the lowest potassium level.

Appearance of the electrocardiographic signs of hypopotassemia was not prevented by disturbances of concentration of other plasma electrolytes or by blood pH. Hypocalcemia and the resultant lengthening of the Q-T interval occasionally caused difficulty because of merging of the T wave with the U wave. Hypopotassemia alone did not influence the Q-aT, Q-T, or Q-aU intervals.

Recognition of the hypopotassemia pattern often was difficult in the presence of tachycardia, which causes decreased amplitude of the U wave as well as merging of the P wave

with the U wave. Attention is directed to the tilted P wave, a previously unrecognized sign of U wave prominence, which may cause suspicion of hypopotassemia, despite tachycardia.

Evidence concerned with the basic cause of the electrocardiographic signs of hypopotassemia is discussed. The plasma potassium level is considered to be the important factor, either directly or by its large effect on the ratio of extracellular to intracellular myocardial potassium concentration.

Acknowledgment

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Summario in Interlingua

In 50 patientes hypokalemic 2 derivationes electrocardiographic (generalmente II e V_3) esseva analysate con respecto al sequente signos de hypokalemia: (1) Amplitude del unda U plus que 1 mm, (2) proportion del amplitudes de undas U a T plus que 1 in le derivation con le plus alte unda U, e (3) depression del segmento S-T plus que 0,5 mm. Secundo le numero de signos representate in le 2 derivationes, le electrocardiogrammas esseva designate como *typic* de hypokalemia (3 signos o plus), *compatibile* con hypokalemia (2 signos, o 1 signo relationate al unda U), e *non-diagnostic* pro hypokalemia (0 signos o solmente depression del segmento S-T in 1 del derivationes).

Esseva trovate un correlation inter le configuration electrocardiographic e le concentration de kalium in le plasma. In un serie de 17 patientes con nivellos de kalium de inter 2,0 e 2,7 mEq/l, 78 pro cento habeva electrocardiogrammas typic de hypokalemia. In 20 patientes con nivellos plasmatic de kalium de inter 3,0 e 3,49 mEq/l, 90 pro cento del registrationes esseva non-diagnostic o solmente compatibile con hypokalemia. In 4 subjectos, 6 signos esseva presente in le 2 derivationes. Omne iste patientes esseva in le gruppo con le plus basse nivellos de kalium.

Le presentia del signos electrocardiographic de hypokalemia non esseva prevenite per disturbationes del concentration de altere electrolytos in le plasma o per le pH del sanguine. Hypocalcemia e le resultante prolongation del intervallo Q-T causava certe difficultates in alicun casos a causa del fusion inter unda T e unda U. Hypokalemia sol non influentiava le intervallos Q-aT, Q-T, o Q-aU.

Le recognition del configuration de hypokalemia esseva frequentemente difficile in le presentia de tachycardia, que causa non solmente un reduction del amplitude del unda U sed etiam un fusion del undas P e U. Es signalate le phenomeno del basculate unda P, un previemente non recognoscite signo de prominentia del unda U. Isto pote causar suspicion de hypokalemia in despecto del presentia de tachycardia.

Es discutite materiales concernite con le causa fundamental del signos electrocardiographic de hypokalemia. Le nivello de kalium in le plasma es considerate como le factor saliente, o directemente o indirectemente in consequentia de su grande effecto super le proportion extra- a intracellular in le concentration de kalium myocardial.

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Intracardiac Phonocardiography in Man

By David H. Lewis, M.D., George W. Deitz, M.D., John D. Wallace, A.B., and James R. Brown, Jr., B.S.E.E.

This paper describes a new method for the detection of sound from within the heart in man. It employs the technic and equipment of underwater listening developed and used by the Navy in antisubmarine warfare. Records are shown to illustrate the localization of heart sound production to an extent not possible by phonocardiograms from the chest wall. The technic has proved helpful in the evaluation of patients with valvular and congenital heart disease.

THE purpose of this paper is to describe a new method for the detection of sounds from within the human heart. Records will be shown to illustrate that this technic enables localization of sound production to an extent not heretofore obtainable. By virtue of this property and by recording the sounds from their point of origin, new avenues of investigation of the production and transmission of sounds and murmurs are now available.

These investigations were made possible by the application to medicine of acoustic technology developed for undersea warfare. The technic was simply that of underwater listening, the passive phase of sonar. The transition from antisubmarine warfare to phonocardiography involved mainly subminiaturization of the transducer and adaptation of the amplifiers to the recording instruments used in routine clinical phonocardiography.

Methods

The technical aspects of this work have been reported previously and will only be referred to briefly.[1] The transducer is a hollow, circular cylinder of activated barium titanate. The activation process was carried out by a methodology developed by Wallace[2] and imparts to the ceramic the qualities of a piezoelectric crystal. Catheters were made by drawing the transducer with its attached cable back into nonirritant plastic tubing.* The transducer and cable were coated with silicone oil to provide lubrication for the insertion and also to provide acoustic coupling between the outer wall of the ceramic and the inner wall of the plastic tubing. The end of the catheter was then sealed chemically. In the present study 2 types of catheters have been used. The first was a single-lumen catheter for sound determinations alone and was approximately a no. 5F in size. The second was a double-lumen catheter using the sound element of the single-lumen catheter and having the other lumen for the usual pressures and sampling. Its size was approximately that of a no. 7½F catheter. In both types, the ceramic at the tip has been made ½-inch long.

The signal from the catheter was fed into a cathode follower-preamplifier unit designed specially for this study. This unit allowed the sounds to be recorded on the phonocardiographic apparatus available in our laboratory, by matching impedances and by several stages of amplification. The records were taken on the Sanborn Twin Beam photographic instrument. Tape recordings were also made with the Cambridge Educational Electron Cardioscope at a tape speed of 1⅞ inches per second. These were made primarily for sound spectrographic analysis by the technic described by McKusick et al.[3] and for comparison of intracardiac sounds with sounds heard on the chest wall as to duration, amplitude, and frequency. These studies will be reported in a subsequent communication.

The subjects of this study, the first 41 patients on whom intracardiac sounds were determined, were all patients from the wards and clinics of the Philadelphia General Hospital and the heart sound studies were done in conjunction with routine cardiac catheterization. The addition of intracardiac phonocardiography to the technic of cardiac catheterization alters the latter procedure very little. Two features of the technic of intracardiac phonocardiography are worthy of note: since the barium titanate is inactivated by autoclaving,† the catheters must

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Abstracted, Circulation **14:** 967, 1956.

* Tygon tubing, obtained from the United States Stoneware Company, Akron, Ohio.

† Catheters are being developed using a transducer with a higher temperature tolerance that will permit autoclaving.

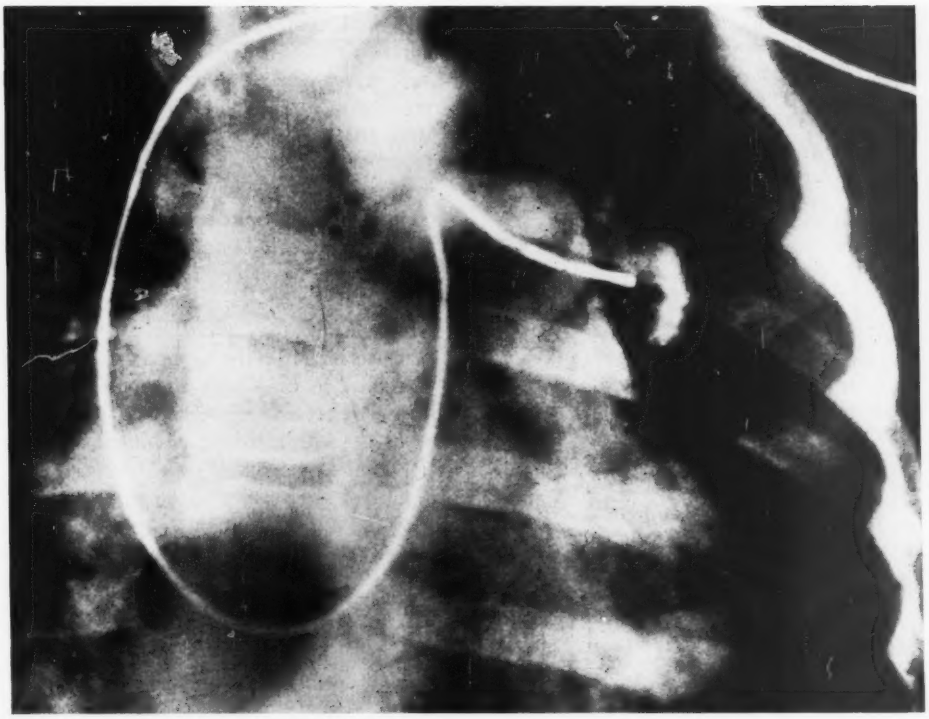

FIG. 1. JLB, 4-year-old girl. Spot film of single-lumen sound catheter with tip in the left pulmonary artery. The transducer at the tip is radiographically more dense than the rest of the catheter.

be sterilized in an antiseptic solution;* since the voltage output of the transducer is very small, special precautions must be taken to reduce electric interference. In our laboratory this has been obtained by careful grounding of all equipment and the patient, by making the sound catheters as short as possible, and by isolating the cathode follower-preamplifier unit in grounded aluminum foil. For the routine cardiac catheterization, pressures were determined with the Sanborn electromanometer. Blood samples were analyzed for oxygen content by the technic of Van Slyke and Neill[4] and gas samples by the technic of Scholander.[5] Cardiac outputs were done by the direct Fick principle with blood taken from the pulmonary artery for the mixed venous sample.

Since the sound catheter has a barium titanate element at the tip and has a metallic cable, it is visible by fluoroscopy. Figure 1, taken at the time of catheterization of the left pulmonary artery shows that the barium titanate transducer at the tip is radiographically more dense than the rest of the catheter.

* We have used Detergicide obtained from the United States Catheter and Instrument Company, Glens Falls, N. Y.

RESULTS

Table 1 shows the diagnoses of the patients. The cardiac rhythm was normal in 37 and showed atrial fibrillation in 4. The intracardiac sounds in each patient are not described; since the number in each group is small, a detailed correlation is not justified. In this preliminary presentation we have chosen to discuss the various auditory events of the normal heart cycle, the abnormal sounds, and finally the heart sounds of congenital heart disease. The salient features of each record are given with each illustration.

First Heart Sound. In all of the patients the first heart sound was heard throughout the lesser circulation. It was heard in both venae cavae near the heart, within the heart itself, and throughout the pulmonary tree, even with the catheter tip in the "wedge" position. With few exceptions, the maximal intensity was in the right ventricle (fig. 2). When differences in the intensity within the right ventricle could

TABLE 1.—*Clinical Diagnosis of Forty-One Patients*

Clinical Diagnosis	Number of Patients	
Normal	3	
Pulmonary tuberculosis, normal heart	5	
Rheumatic heart disease	9	
with mitral stenosis		3
with mitral insufficiency		1
with mitral stenosis and insufficiency		3
with aortic stenosis		1
with mitral stenosis and insufficiency and possible aortic insufficiency		1
Congenital heart disease	12	
patent ductus arteriosus		3
ventricular septal defect		4
ventricular septal defect with pulmonary stenosis		1
pulmonary stenosis		2
atrial septal defect or anomalous venous return		1
tricuspid atresia		1
Paget's disease of bone	2	
Pulmonary fibrosis and emphysema	2	
Idiopathic dilatation of pulmonary artery	1	
Pulmonary arteriovenous fistula, possible	1	
Carcinoma of lung	1	
Dystrophic heart disease with possible rheumatic heart disease	1	
Lung abscess	2	
Agenesis of one lung	1	
Idiopathic cardiac hypertrophy	1	

be appreciated, it was found to be louder in the outflow tract than in the inflow tract (fig. 2*B*). Of very great interest to us was the observation that the first heart sound was never loudest in intensity in the region of the tricuspid valve. On occasion its intensity here (fig. 2*B*) was markedly reduced but usually to a lesser extent. These observations on the first heart sound suggested that we were hearing events from the left ventricle and that closure of the tricuspid valve was not a major contribution to the make-up of this sound.

In addition to observations on the over-all intensity of the first heart sound, differences in the intensity of components of the first heart sound have been noted depending on the position of the catheter tip. For example, in figure 3, the major component of the first heart sound begins 0.06 to 0.07 second after the Q wave and occurs during the early pressure rise in the right ventricle. * Most, if not all, of this component is over before the ventricular pressure has reached the level of the end-diastolic pressure in the pulmonary artery. At the time that this sound is produced, therefore, the pulmonic valve is closed. In the pulmonary artery, in contradistinction, the first major component of sound begins 0.14 second after the Q wave and is on the ascending limb of the pulmonary artery pressure curve. In the tracing taken in the pulmonary artery a few vibrations of low intensity are seen 0.06 to 0.07 second after the Q wave, and correspond, therefore, in time with the loud sound heard in the right ventricle. There is, then, a sound occurring with the onset of ventricular contraction that is loud in the right ventricle and is of much less intensity in the pulmonary artery. It would appear that this loud sound is transmitted poorly through the closed pulmonic valve. This same phenomenon, namely, that loud components of the first heart sound occur earlier in the right ventricle than in the pulmonary artery, is also present in figures 2*A* and 2*B*.

Second Heart Sound. In all of the patients, the second heart sound, like the first heart sound, was heard throughout the lesser circulation. Its maximal intensity was found to be in the pulmonary artery. There was little difference in intensity throughout the pulmonary tree, even with the catheter tip in the "wedge" position. During the withdrawal of the catheter from the pulmonary artery into the right ventricle, the intensity of the second heart sound decreased suddenly and the intensity of the first heart sound increased (fig. 2*A*). At the time of catheterization, the person listening to the intracardiac sounds was able to detect this change in the position of the catheter tip by the nature of the sounds without knowledge of the intravascular pressures or fluoroscopic image. The second heart sound could be heard in the inflow tract of the right ventricle and in the right atrium but was almost always much less intense. Of interest is the observation

* The photographic records are displayed as they were obtained. To correct for the time delay in pressure registration as compared with sounds, the pressure curve should be moved to the *left* 0.01 second.

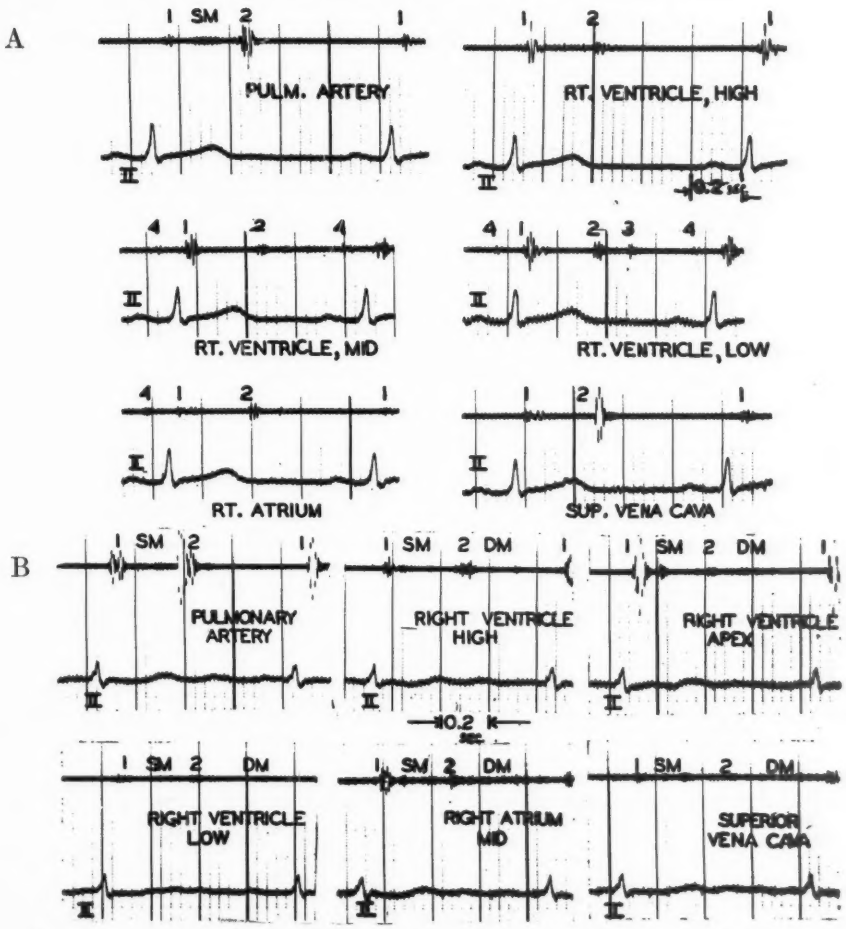

FIG. 2. Sounds from the lesser circulation. In each strip the upper record is of intracardiac sounds and the lower record is lead II of the electrocardiogram; the time lines are 0.04 and 0.2 second respectively. *A*. NC, 28-year-old man. Pulmonary tuberculosis, left upper lobe. Normal heart; no murmurs. The first heart sound is heard at all locations and is loudest (i.e., greatest amplitude) in the right ventricle. The second heart sound is heard at all locations and is loudest in the pulmonary artery and superior vena cava; there is a marked drop in intensity in going from the pulmonary artery to the outflow tract of the right ventricle. The third heart sound is heard in the right ventricle and is probably present in the tracing from the right atrium; it is loudest in the inflow tract of the right ventricle. The fourth heart sound is heard in the right atrium and right ventricle. There is a midsystolic murmur in the pulmonary artery. *B*. CA, 47-year-old woman. Rheumatic heart disease with mitral stenosis and insufficiency and atrial fibrillation. The first heart sound is heard in all locations and is loudest in the right ventricle; in the region of the tricuspid valve (right ventricle low) the intensity is much less than at the apex of the right ventricle. The second heart sound is heard in all locations and is loudest in the pulmonary artery; its intensity drops abruptly from the pulmonary artery to the outflow tract of the right ventricle. No fourth heart sound is heard at any location. Systolic and diastolic murmurs are present at all locations with the exception that the diastolic murmur is not heard in the pulmonary artery.

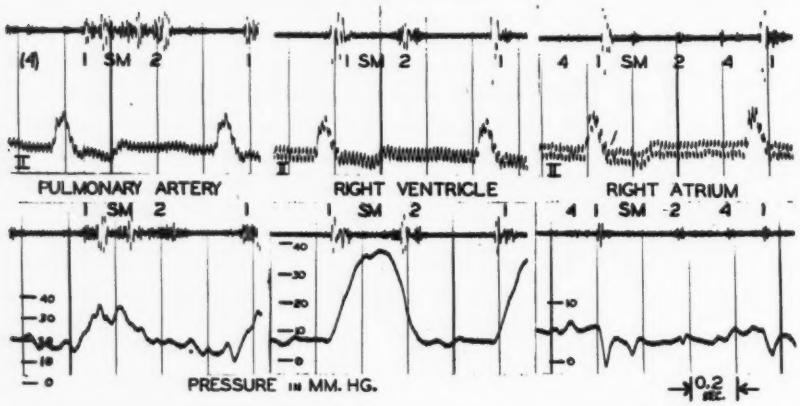

FIG. 3. Intracardiac sounds and intravascular pressures. DS, 39-year-old woman. Rheumatic heart disease with mitral insufficiency and left bundle-branch block. Top row: intracardiac sounds and lead II of the electrocardiogram. Bottom row: intracardiac sounds and intravascular pressures from the pulmonary artery, right ventricle, and right atrium. The first heart sound is louder in the right ventricle than it is in the pulmonary artery; the initial loud component heard in the ventricle and in the atrium occurs at the onset of ventricular systole and is virtually complete before the ventricular pressure has reached the level of end-diastolic pulmonary artery pressure; it occurs, therefore, before the pulmonic valve has opened. The fourth heart sound occurs at the peak of the "a" wave in the right atrial tracing. The peak intensity of the systolic murmur in the pulmonary artery occurs at the peak of the pulmonary artery pressure.

that in some cases the second heart sound became loud again as the catheter was withdrawn into the superior vena cava (figs. 2*A* and 2*B*). We think that this difference is related to the proximity of the vena cava to the right pulmonary artery.

In addition to observations on the over-all intensity of the second heart sound, we have also been interested in the site of origin of the second heart sound heard in the pulmonary artery. This point is illustrated in figure 4*B* which shows phonocardiograms taken on a 41-year-old woman with rheumatic heart disease with mitral stenosis and insufficiency and possible aortic valvular disease. Roentgen examination showed slight left atrial enlargement, straightening of the left heart border, and prominence of the pulmonary artery. At cardiac catheterization, the pressure in the pulmonary artery was 20/9 mm. Hg, with a mean pressure of 13 mm. Hg. Systemic blood pressure was within normal limits. On auscultation, as seen in the upper tracings, which are precordial phonocardiograms, an accentuated P_2 was described. However, as seen in the lower tracing, the second heart sound *in* the pulmonary artery was not accentuated. Since the second heart sound *in* the pulmonary artery was not loud, the loud second heart sound heard at the pulmonic area on the chest was not due to pulmonic closure but to aortic closure. Others[6] have suggested that in some cases, the loud second heart sound heard at the pulmonic area is due to closure of the aortic valve. We think that this record is strong evidence in favor of this viewpoint and believe that the location of the sound results from rotation of the heart and great vessels.

Third Heart Sound. This sound has been present in only a few of the cases studied to date (figs. 2*A*, 5*B*, and 6*D*). In 1 case a third heart sound was noted in the chest phonocardiograms taken at the apex. A third heart sound was also noted in the intracardiac recordings. In 2 cases a third heart sound was noted in the intracardiac phonocardiograms but was not recorded in those taken from the precordium. The third heart sound has been heard in the right ventricle and in the right atrium. It appears to be of greatest intensity in the inflow tract of the right ventricle (fig. 2*A*), but has been heard with almost equal

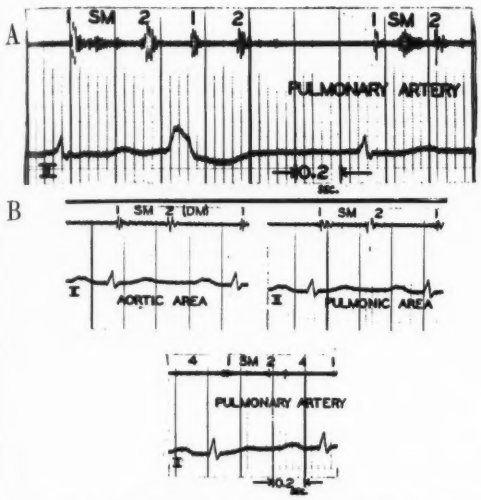

FIG. 4. Pulmonary artery phenomena: the midsystolic murmur and the second sound. *A*. CA, 47-year-old woman, same patient as in figure 2*B*. Here, a premature ventricular contraction does not have the normally occurring systolic murmur, while the following normally conducted beat after a longer filling time has a systolic murmur of greater than normal intensity. *B*. OG, 41-year-old woman. Rheumatic heart disease with mitral stenosis and insufficiency and possible aortic valve disease. Pulmonary artery pressure 20/9 mm. Hg with a mean of 13 mm. Hg. The upper row of tracings shows chest phonocardiograms taken at the aortic and pulmonic areas and demonstrates that P_2 was accentuated and louder than A_2. The bottom tracing taken of intracardiac sounds in the pulmonary artery shows that here the second sound is not accentuated.

intensity in the right atrium (fig. 6*D*). No conclusions have been reached as to the etiology of this sound from the observations currently available.

Fourth Heart Sound. In all patients who had atrial contractions (i.e., a P wave in the electrocardiogram) a fourth heart sound was heard in some part of the heart. In a few cases it could be heard in all locations (figs. 3, 4*B*, and 6*D*), but in the remainder it was localized to the atrium and either diminished markedly or disappeared entirely as the catheter was moved into the ventricle or the venae cavae. On the other hand, it was unusual to observe a fourth heart sound in the chest phonocardiograms.

Frequently the sharp localization of the fourth heart sound within the heart was surprising. Figure 5*A* shows a loud fourth heart sound in the right atrium almost the intensity of the first heart sound and yet it is not heard in the superior vena cava just above the right atrium. In figure 5*B* when the tip of the catheter is in the right atrium near the tricuspid valve, there is a definite fourth heart sound, which is inaudible when the transducer lies at the mid-atrial level. Figures 5*A* and 5*B* suggest that the direction of blood flow may have something to do with carrying the sound away from certain parts of the heart. However, in figure 6*C* are records taken on either side of the tricuspid valve showing a clearly audible fourth heart sound on the atrial side, which is virtually inaudible on the ventricular side. This is occurring at a time when the tricuspid valve is open and blood is flowing from the right atrium into the right ventricle.

In much the same way that changes in the nature of the first and second heart sounds allow the listener to tell the transition from the pulmonary artery to the right ventricle, the appearance of a well-defined fourth heart sound allows the listener to note the transition from the right ventricle to the right atrium. The fact that the sound is loudest in the right atrium leads us to conclude that it is related to atrial events. It is related to atrial contraction as judged by the fact that the sound occurs at the peak of the "a" wave of the atrial pressure pulse (fig. 3, right atrium) and by the fact that the sound is not heard in patients with atrial fibrillation (fig. 2*B*). Whether it is due to muscle contraction or alterations in blood flow that occur during atrial systole, we are unable to state at the present time.

Effect of Respiration. Variations in the intensity of the first and second heart sounds due to respiration have been difficult to assess. In most cases, these sounds seemed unaffected by respiration. In contrast, respiration caused marked variations in the intensity of the fourth heart sound. Figures 5*D* and 6*D* (right atrium) show intracardiac phonocardiograms at the onset of respiration which, as expected, increased the intensity of the fourth heart sound. For comparison, the lower strip in figure 5*D* shows no fourth heart sound heard on the precordium.

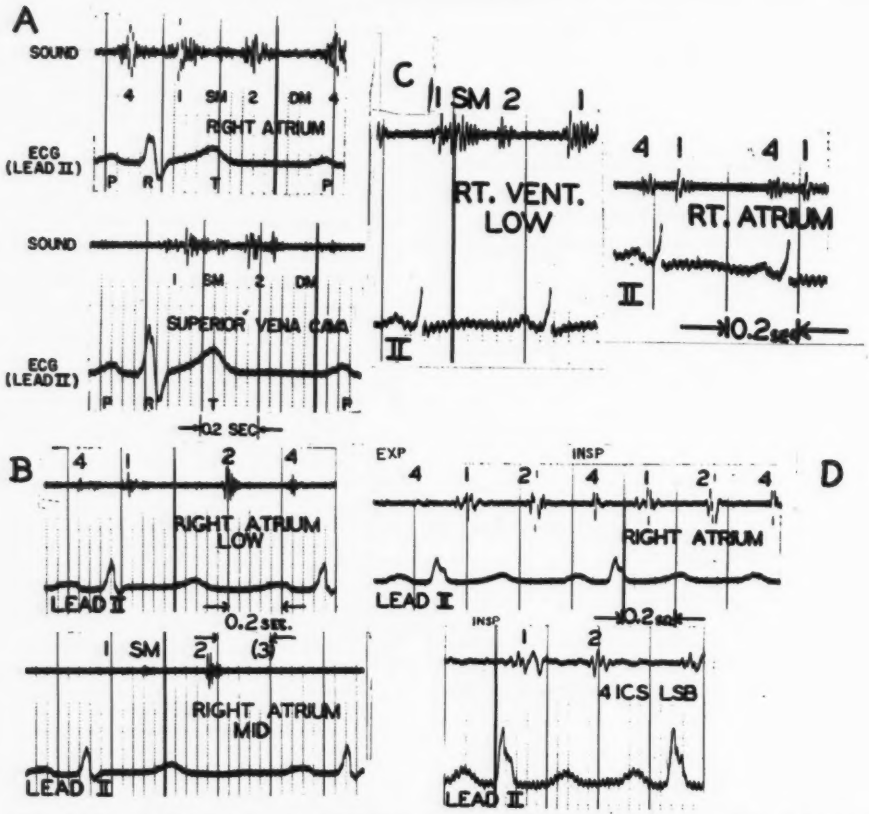

FIG. 5. The fourth heart sound. *A*. TC, 24-year-old man. Idiopathic dilatation of the pulmonary artery. There is a loud fourth heart sound in the right atrium, which is not heard in the superior vena cava just above the right atrium. *B*. JC, 24-year-old woman. Rheumatic heart disease with mitral stenosis. A fourth heart sound is present in the right atrium near the tricuspid valve that is not heard at the mid-atrial level. *C*. SMcC, 2-year-old girl. Normal heart. A fourth heart sound is heard on the atrial side of the tricuspid valve and is very faint on the ventricular side. *D*. JB, 56-year-old man. Chronic pulmonary fibrosis and emphysema, dilated pulmonary artery, pulmonary artery pressure 30/15 mm. Hg, with a mean pressure of 24 mm. Hg. In the top strip intracardiac sounds from the right atrium show variations in intensity of the fourth heart sound due to respiration. In the bottom strip no fourth heart sound is heard on the precordium.

Murmurs. Where murmurs were heard on the precordium, they were also heard within the heart (figs. 2*B*, 3, 4*B*, 5*A*, 5*C* and 7). The diastolic murmur of mitral stenosis, in patients who clinically and by cardiac catheterization did not have tricuspid valvular pathology, was heard in the right ventricle and in the right atrium but was not heard in the pulmonary artery. In those cases with the apical systolic murmur of mitral insufficiency, this murmur was also heard in the right ventricle and in the right atrium but was loudest in the pulmonary artery. The difference in the transmission of the 2 murmurs to the pulmonary artery was somewhat puzzling until it was observed that in those cases in which there were no murmurs present in the chest phonocardiograms and, indeed, elsewhere in the heart, there was a systolic murmur in the pulmonary artery (fig. 2*A*). In every tracing thus far obtained there has been a systolic murmur in the pulmonary artery. We believe that this localization is due to blood flow. This is based on the observations that (a) the peak of intensity of the

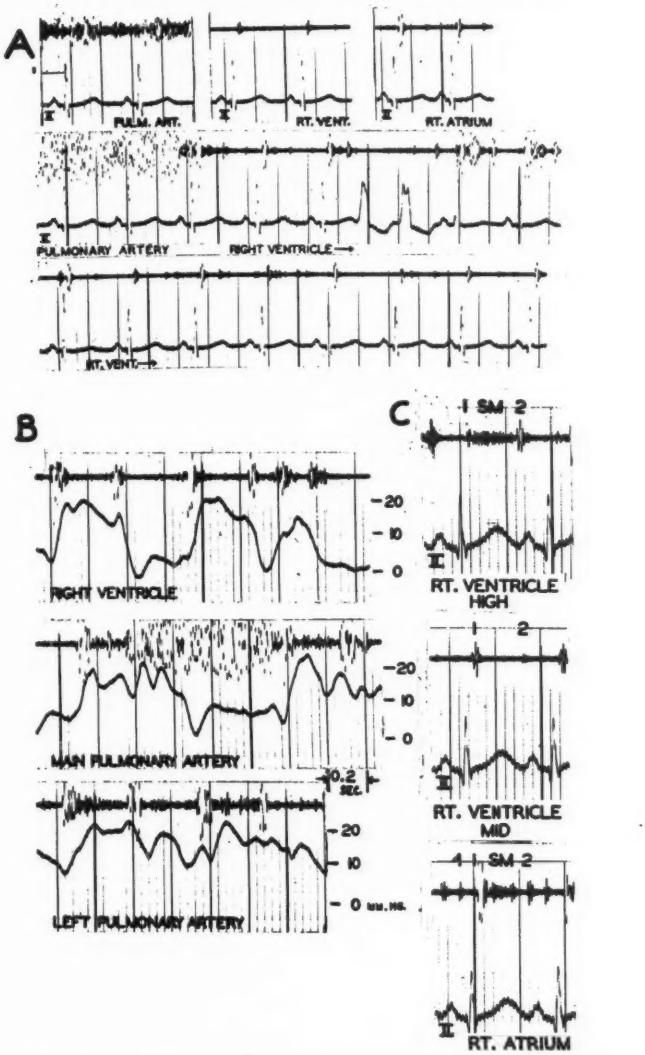

FIG. 6. Congenital heart disease. *A*. RC, 2-year-old boy. Patent ductus arteriosus. Top row: intracardiac sounds and lead II of electrocardiogram from the pulmonary artery, right ventricle, and right atrium. Middle and bottom row: continuous tracing of sounds and electrocardiogram. A machinery murmur is heard in the pulmonary artery that is not heard in the right ventricle or right atrium. Continuous tracing demonstrates that the change in the intracardiac sounds occurs abruptly at the pulmonic valve. *B*. NM, 18-year-old girl. Patent ductus arteriosus. Continuous tracing of intracardiac sound and intravascular pressure as the catheter is advanced rapidly from the outflow tract of the right ventricle into the descending branch of the left pulmonary artery. In the main pulmonary artery in the region of the left pulmonary artery is a loud machinery murmur that is not heard in the right ventricle or more distally in the left pulmonary artery. *C*. EW, 3-year-old boy. Ventricular septal defect, possible pulmonary stenosis. There is a systolic murmur high in the right ventricle that is not heard at the midventricular level.

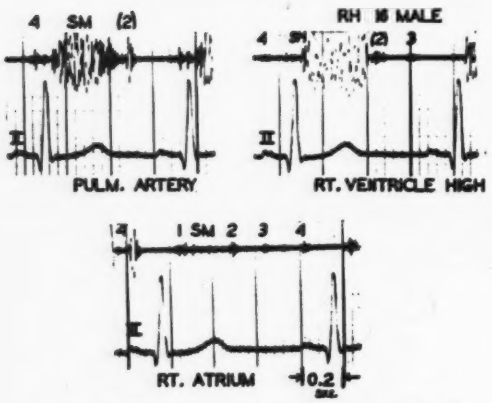

FIG. 6. *D.* RH, 16-year-old boy. Isolated infundibular stenosis. A loud, long harsh systolic murmur is present in the pulmonary artery which is louder in the outflow tract of the right ventricle and which is much less intense in the atrium.

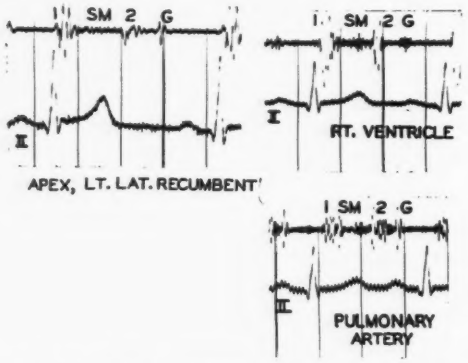

FIG. 7. The gallop sound. HJ, 26-year-old man. Progressive muscular dystrophy (adult type). Dystrophic heart disease, and possible rheumatic heart disease. On the left, chest phonocardiogram taken at the apex with the patient in the left lateral recumbent position shows the loud gallop. On the right, intracardiac sounds from the right ventricle and pulmonary artery. The gallop sound is heard in both locations; in the pulmonary artery the sound is shorter, louder, and of a higher frequency than in the right ventricle.

murmur occurs at the peak of the pulmonary artery pressure curve (fig. 3, pulmonary artery), and (b) as seen in figure 4*A* a premature ventricular contraction is not associated with the normally occurring murmur while the next normally conducted beat after a longer filling time has a systolic murmur of greater intensity than that normally heard.

Gallop Sound. In 1 patient there was a loud gallop sound present at the time of cardiac catheterization. In figure 7, on the left, is the chest phonocardiogram taken with the patient in the left lateral recumbent position, which accentuated the gallop. The tracings on the right show that this sound was heard in both the right ventricle and the pulmonary artery. In the right ventricle, the sound is of a low pitch and on auscultation during catheterization it sounded very much like the gallop heard on the precordium. In the pulmonary artery the sound is shorter in duration and has a "snappier" quality. It would appear that the differences in the duration, intensity, and pitch are due to filtering of the sound by the various vascular structures.

Congenital Heart Disease. All the above results indicate that this new technic of heart sound registration localizes sound production to an extent not previously obtainable. This immediately suggests a possible usefulness in congenital heart disease, and, indeed, the most striking examples of localization have been seen in these cases.

Figure 6*A* shows tracings from a 2-year-old boy subsequently proved at operation to have a large patent ductus arteriosus. In the pulmonary artery there is a machinery murmur completely obscuring the first and second heart sounds. In the right ventricle and right atrium the sounds are well heard with little or no murmur. The 2 lower strips are a continuous tracing as the catheter was pulled back from the pulmonary artery into the right ventricle and show an abrupt transition at the pulmonic valve.

In the above case the typical murmur on the precordium left no doubt as to the diagnosis. In 1 of our patients, however, a murmur was heard at the pulmonic area and up under the left clavicle that was suggestive of patent ductus arteriosus but was not typical. Some observers doubted the presence of a ductus and suggested such possibilities as venous hum, coarctation of the pulmonary artery, pulmonary arteriovenous fistula, and a congenital anomaly of the pulmonic valve. Cardiac catheterization was completely normal. There was no evidence for a left-to-right shunt in the

pulmonary artery nor was there evidence for the other possibilities suggested. Figure 6*B* is a continuous tracing taken as the sound catheter was advanced rapidly from the outflow tract of the right ventricle to the distal left pulmonary artery. In the main pulmonary artery near the left pulmonary artery a typical machinery murmur of patent ductus arteriosus was heard that was not present elsewhere in the pulmonary tree nor could it be heard within the heart itself. On this basis a diagnosis was made of a small patent ductus arteriosus, which was subsequently shown to be present at operation.

Our studies in congenital heart disease are by no means complete and the exact diagnosis in many cases is at present unproved surgically. Two examples of systolic murmurs in association with congenital heart disease are shown in the last 2 figures.

Figure 6*C* shows recordings on a boy whose findings at catheterization indicated a high ventricular septal defect and probable pulmonary stenosis. High in the ventricle is a systolic murmur that is not heard in the lower portion of the ventricle. Figure 6*D* shows tracings from a boy in whom catheterization indicated isolated infundibular stenosis of a mild degree. There is a loud, long systolic murmur in the pulmonary artery and in the outflow tract of the right ventricle. Through a technical error the sounds from the inflow tract of the right ventricle were not recorded, but auscultation during the procedure indicated a marked drop in the intensity of the murmur in this region. This is also seen in the atrial recording. In these 2 cases, therefore, the characteristic murmur was heard best at the place where the lesion was located.

Discussion

To the best of the authors' knowledge this is the first medical report of this new method for the detection of sounds from within the human heart. However, this is not the first report on intracardiac phonocardiography. In 1954 Yamakawa et al.[7] reported on studies of intracardiac sounds. Their studies were done in dogs and in "three human beings, in one of which the catheter microphone reached the pulmonary artery and then heart sounds at various parts in the heart were recorded on the tape recorder." However, no records of the sounds obtained in these patients are published in this report. They used a condenser microphone at 1 end of a catheter with the blood and body as the second electrode. This compromise imposed such severe limitations on the results that they say in their summary, "when the catheter tip is placed in the blood stream, chiefly coarse sounds due to a blood whirlpool are recorded, and when the tip is contacted with the inner wall of the heart, chiefly vibrations of a solid structure are recorded. These latter are thought to be similar to the heart sounds obtained from the chest wall." In our technic the barium titanate transducer, both sides of which are isolated from the blood, eliminated this problem. In our studies the best records were obtained when the transducer was free in the blood stream. Little or no "whirlpooling" sounds were noted though some of the high frequency noise may have been due to blood flow. When the catheter tip was in contact with the inner wall of the heart or the valves, loud knocking sounds were obtained that were similar to those obtained when the catheter tip was flicked with the finger nail. We have considered these to be artifacts. From a technical standpoint, too, research on underwater microphones indicates that the fidelity and frequency response of the barium titanate hydrophone, for this purpose, is far superior to the condenser microphone and especially so when the medium in which the sounds are produced is used as one side of the condenser.[8]

In the studies to date we have recorded intracardiac sounds at the time of cardiac catheterization.* In these preliminary investigations we have not considered ourselves justified in doing this procedure for intracardiac sounds alone when there was no indication for cardiac catheterization. In patients in whom cardiac catheterization was indicated we thought that it was justifiable to take the time

* Three studies were done to assess the feasibility of introducing the single-lumen sound catheter by percutaneous needle puncture. Two were done on patients in whom catheterization was indicated but who were opposed to a cut-down procedure and 1 was done on the senior author.

to record intracardiac sounds. The results have been rewarding in at least 1 case where intracardiac phonocardiography pointed out the diagnosis very clearly. In our hands this procedure has not increased the risk of cardiac catheterization. We believe that there is sufficient merit to this technic to make it part of the routine cardiac catheterization. At the present time steps are being taken to make the equipment available through commercial channels.*

It is clear that we have barely scratched the surface of the amount of information to be learned from this technic. In the realm of studies of immediate clinical importance, further work is being carried out on the value of this technic in the diagnosis of congenital heart disease and in the diagnosis of valvular lesions in patients considered to be candidates for valvular repair. In the realm of basic studies, work is being carried out on the absolute intensity of sounds from inside the heart and a comparison of intracardiac sounds with precordial sounds as to intensity, frequency, and duration. In this way it is hoped that further knowledge as to the method of production of heart sounds and murmurs within the heart and transmission to the chest wall will be obtained.

It should also be clear that a study of intracardiac sounds from the right side of the heart alone is incomplete. Studies in dogs indicate that the intensity of sounds is far greater from the left side than from the right side of the heart.[1] There is no reason to suspect that this may not be true for man. We have rejected the idea of retrograde arterial passage with our present catheter because of the likelihood of valvular damage. Sounds from the left heart in man will be studied by the usual technic of left heart catheterization[9] upon completion of a special catheter.

Summary

A new technic for the detection and study of heart sounds from within the heart in man has been described. This method uses the technic of underwater listening developed for undersea warfare and applies it directly to the study of heart sounds. These studies can be done at the time of right-sided cardiac catheterization with no additional hazard to the patient.

The characteristics of the heart sounds in the lesser circulation have been described. The first heart sound is loudest in the right ventricle. The second heart sound is loudest in the pulmonary artery. The third heart sound is loudest in the right ventricle. The fourth heart sound is loudest in the right atrium.

This technic is capable of localizing heart sounds and murmurs to an extent not heretofore obtainable. The addition of this instrument will materially increase knowledge of the origin of heart sounds and murmurs. The application of this technic to the other studies done at the time of cardiac catheterization should be of definite help in the diagnosis of congenital heart disease.

Summario in Interlingua

Es describite un nove technica pro le detection e le studio de sonos cardiac ab intra le corde human. Le methodo usa le technica del ascoltamento subaquatic disveloppate pro le objectivos del belligerentia submarin e applica lo directemente al studio del sonos cardiac. Iste studios pote esser effectuate al tempore del execution de catheterisation dextero-cardiac sin hasardo additional pro le patiente.

Le characteristicas del sonos cardiac in le circulation minor es describite. Le prime sono cardiac es le plus intense in le ventriculo dextere. Le secunde sono cardiac es le plus intense in le arteria pulmonar. Le tertie sono cardiac es le plus intense in le ventriculo dextere. Le quarte sono cardiac es le plus intense in le atrio dextere.

Iste technica pote localisar sonos e murmures cardiac a grados de precision non previemente effectuabile. Le disponibilitate de iste instrumento va servir a augmentar considerabilemente nostre cognoscentias in re le origine del sonos e murmures cardiac. Le application de iste technica al altere studios interprendite al

* Catheters and amplifiers are available commercially through the American Electronic Laboratories, Inc., Philadelphia, Pa.

tempore del catheterisation cardiac debe provar se de adjuta definite in le diagnose de congenite morbo cardiac.

ACKNOWLEDGMENT

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De Bakey, M. E., Cooley, D. A., and Creech, O., Jr.: Aneurysm of the Aorta Treated by Resection. J.A.M.A. **163:** 1439 (April 20), 1957.

This report summarizes a 5-year experience in which 313 aortic aneurysms were resected. Surgical technics involved simple excision in the case of saccular aneurysms, and additional grafting in fusiform lesions. When the arch of the aorta is cross-clamped during the resection, a temporary shunt around the occluded segment or hypothermia is employed to protect particularly the central nervous system from ischemic effects. The frequent involvement of one or more major abdominal aortic branches by the aneurysm no longer prevents successful resection, and therefore diagnostic aortography is seldom needed. In dissecting aneurysms the false passage usually is led back into the aortic lumen proximally and distally it is obliterated; less commonly the dissecting area is totally excised. The over-all operative mortality rates have been 31 per cent for 83 thoracic aneurysms, 33 per cent for 27 ruptured abdominal aneurysms, and 8 per cent for 203 nonruptured abdominal ones. Factors increasing these mortality rates have been technical inexperience, patients over 60 years of age, and the presence of hypertension or heart disease. Follow-up studies of patients surviving abdominal operation for periods up to 3½ years have shown in general excellent relief of symptoms, good circulatory maintenance, and a significant increase in survival rates.

ROGERS

Effects of Upright Posture and Exercise on Pulmonary Hemodynamics in Patients with Central Cardiovascular Shunts

By ROBERT A. BRUCE, M.D., AND GREGORY G. JOHN, M.D.

With the assistance of Curt A. Wiederhielm, Charlotte Hamilton, Claire Morgan, R.N., and Elizabeth Kendall, R.N.

Previous hemodynamic studies of patients with septal defects, or patent ductus arteriosus, have been made with the patient recumbent in the horizontal posture. Our studies indicate unexpected changes in pulmonary blood flow with the upright posture, and often further increments in flow during walking that are different from those reported for exercise in recumbency. It is suggested that such defects reveal the complexity of factors regulating preferential flow under these circumstances.

IN THE course of selecting patients with atrial or ventricular septal defects for surgery, it became apparent that little is known regarding the effects of the upright posture and exercise on the pulmonary hyperemia that is often associated with these lesions. Usually there is recirculation of oxygenated blood through the lungs because of the left-to-right shunt through an uncomplicated septal defect. Whereas in the absence of shunting, cardiac output may decrease on standing[1-3] and increase with effort,[4-7] the corresponding effects in the presence of a shunt have not been well described. This report summarizes our preliminary observations of these effects in carefully selected good risk patients.

MATERIAL AND METHODS

Fifteen patients have been studied; they ranged in age from 7 to 49 years (table 1). Six had atrial septal defects, 4 had ventricular septal defects, 3 had patent ductus arteriosus, and 1 of these was also in the fourth month of pregnancy. Two others, who had no shunts, served as controls. Each was tested for exercise tolerance by walking on a motor-driven treadmill on a 10 per cent grade at 1.7 m.p.h. for 10 minutes, and all were able to do this without evidence of ventricular irritability. Following completion of a diagnostic catheterization of the heart, while sedated with meperidine hydrochloride, each was given 25 mg. of ephedrine sulfate intramuscularly to combat faintness and nausea due to orthostatic hypotension that frequently develops when patients so sedated and catheterized assume the upright posture. None had any untoward effects from this supportive therapy, and the subsequent exercise performance was usually comparable to the initial test. All were carefully supervised, and the precordial electrocardiogram was monitored continuously. Only 2 patients exhibited ventricular premature beats in the upright posture with the tip of the catheter in the right branch of the pulmonary artery. It was not practical to study the effects of both posture and exercise in all patients, but 10 patients were studied with respect to either sitting upright or walking.

Oxygen consumption ($\dot{V}_{O_2}$), corrected to STPD, was derived from gasometer measurements of ventilation (BTPS) over a period of 3 to 9 minutes, and from Scholander analyses of expired air while the patient was in a "steady state" and breathing room air through a mouth piece (table 2).[8] Blood samples were analyzed for oxygen content (C) by the Van Slyke-Neill technic.

Blood flows (Q) were derived according to the Fick principle[9]:

$$\text{Total pulmonary blood flow} = Q_{TF} = \frac{\dot{V}_{O_2}}{C_{PV} - C_{PA}}$$

$$\text{Effective pulmonary blood flow} = Q_{EF} = \frac{\dot{V}_{O_2}}{C_{PV} - C_{LC}}$$

$$\text{Systemic blood flow} = Q_S = \frac{\dot{V}_{O_2}}{C_{FA} - C_{VC}}$$

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These studies have been supported in part by Grants-in-Aid from the National Heart Institute and the Washington State Heart Associations.

Presented at Scientific Session, American Heart Association, Cincinnati, Ohio, October, 1956.

Dr. John was a Trainee of the National Heart Institute, 1955–1956.

Where C_{PV} was assumed to be 99 per cent of oxygen capacity, and C_{VC} represented the average of oxygen contents of blood samples withdrawn from the superior and upper part of the inferior vena cava. Shunt flows were derived as follows:

$$Q_{LR} = Q_{TP} - Q_{EP}$$

$$Q_{RL} = Q_S - Q_{EP}$$

When the patients were supine, 10 cm. above the table top was arbitrarily selected as the zero reference level for intrathoracic pressures, which were measured with a Statham gage (P23D). When the patients were in the upright position the gage was placed near the level of the pulmonic valve as determined by fluoroscopy, with the tip of the catheter just distal to the valve. Since changes in intrathoracic pressure secondary to posture were not measured, the mean pulmonary arterial pressure during walking was determined from the sum of the mean pressure while supine plus the difference observed in changing from sitting to walking with the new zero reference level for the gage. The pulmonary arterial pressures recorded over 2 respiratory cycles were utilized to derive the mean pressure by planimetric integration.

Arterial oxygen saturation was continuously recorded from an ear oximeter by means of Wiederhielm's amplifier and a 10-inch strip recorder.[10]

Results

Changes in Pulmonary Blood Flow with Sitting

All 8 patients with central shunts showed some increase in pulmonary blood flow on

TABLE 1.—*Physical Characteristics and Laboratory Data*

Patient, age, sex, and surf. area	Diag. compl. ECG	Clin. class & PFI	Blood flows while supine L./min.					O_2 Sat. % HgGm. %	0.5 sec. EV vital cap.		Dil. curve A D/A	O_2 cons. ml./M.²/ min.
			TP	EP	S	LR	RL		L	%		
KS	ASD	IA	5.9	4.5	4.7	1.4	0.2	98.0	2.7	84	11.4	109
29M												
1.9	RVH	31.1						14.6	3.2	73	1.3	
SR	ASD	IA	13.1	5.4	6.7	7.7	1.3	92.3	2.2	67	6.0	159
12F												
1.73	RVH	12.4						12.5	3.3	95	2.0	
V McC	ASD	IIB	6.5	3.4	4.7	3.1	1.3	87.8	1.4	61	11.7	150
46M	Emphysema											
1.73	RVH	19.0						15.2	2.3	54	2.4	
PK	ASD	IB	4.6	2.5	2.6	2.1	0.1	88.5	2.7	68	12.2	102
19F												
1.72	RBBB	19.7						13.5	4.0	120	2.9	
PS	ASD	IIB	7.8	2.4	2.7	5.4	0.3	92.6	1.1	34	4.0	108
24F	Inc.											
1.5	RBBB	15.7						12.2	3.2	100	2.5	
JH	ASD	1A	7.5	3.3	3.5	4.2	0.1	96	1.2	43		159
15F												
1.6	RVH	13.3						13.4	2.8	91		
Mean ± S.D.								92.5	1.9	59	9.1	
								±4.6	±.74	±18	±3.5	
1.7 ± 0.14		18.5	7.6	3.6	4.2	4.0	0.6	13.6	3.1	89	2.2	131
		±6.8	±2.9	±1.1	±1.5	±2.3	±0.6	±1.1	±.6	±23	±.54	±27
JG	VSD	IIIC	6.8	6.5	7.5	0.3	1.0	96.0	1.9	53	11.0	242
39M	IS											
1.74	RVH	10.2						14.7	3.6	80	1.2	
WB	VSD	IIIC	4.5	2.8	3.5	1.7	0.7	85.0			4.7	163
23M	PH											
1.61	RHS	7.9						19.1				
RF	VSD	IB	14.8	6.3	6.5	8.5	0.2	98.0	2.5	59	6.8	179
9M	PDA											
2.15	LVH	14.2						13.7	4.2	90	1.3	
JP	VSD	IIIC	2.2	2.2	3.9	0	1.7	77.6	2.8	100		168
5F	PH											
1.45	RVH	9.1						17.2	1.8	64		

TABLE 1.—*Continued*

Patient, age, sex, and surf. area	Diag. compl. ECG	Clin. class # PFI	Blood flows while supine L./min.					O_2 Sat. % HgGm. %	0.5 sec. EV vital cap.		Dil. curve A D/A	O_2 cons. ml./M.²/min.
			TP	EP	S	LR	RL		L	%		
JW	PDA	IIB	8.9	4.9	6.1	4.0	1.2	92.5	1.5	68	11.8	189
49M	Bronchitis											
1.83	1°AV, LBBB	18.0						15.9	2.2	51	1.7	
NA	PDA	IB	7.9	4.8	6.1	3.1	1.3	91.0	1.6	46	9.4	155
21F	Preg.											
1.63	(4 months)	13.7						10.8	3.5	106	0.8	
AK	PDA	IIIC	2.8	2.4	3.4	0.4	1.0	85.4	1.1	58	8.4	142
37F	PH											
1.5	1°AV	14.2						15.3	1.9	67	1.0	
IH	AI	IIIC	3.9		3.9			95.3	1.8	60		134
32F	MIS											
1.54	AF	12.0						12.8	3.0	100		
BW	No	IA	2.4		2.4			86.6	0.6	46	7.6	169
7M	HD											
0.93		14.0						13.1	1.3			

ASD = Atrial septal defect
VSD = Ventricular septal defect
PDA = Patent ductus arteriosus
IS = Infundibular stenosis
AI = Aortic insufficiency
MIS = Mitral insufficiency and stenosis
No HD = No heart disease (functional murmur)
PH = Pulmonary hypertension
AF = Atrial fibrillation
RHS = Right heart "strain"
RVH = Right ventricular hypertrophy
LVH = Left ventricular hypertrophy
1°AV = First degree AV block

# = Functional capacity (N. Y. Heart Assoc.)
PFI = Physical fitness index of tolerance of standardized exercise tests
TP = Total pulmonary blood flow
EP = Effective pulmonary blood flow
S = Systemic blood flow
LR = Left to right shunt
RL = Right to left shunt
EV = 0.5 sec. expiratory volume, (% = per cent of observed VC)
VC = Vital capacity, (% = per cent of predicted for age, sex, and height)
A = Appearance time, sec. ("Normals" = 10.6 ± 2.7 Sec.)

$$D/A = \frac{\text{Disappearance time constant}}{\text{Appearance time}}$$

(where D equals time for fall in concentration to one-half, and normal D/A = 0.5 ± 0.1 sec.)

changing from supine to sitting posture (fig. 1). In 2 of these patients who also had pulmonary hypertension, the changes were negligible, whereas 2 other patients with patent ductus arteriosus complicated by other factors exhibited marked increases in total pulmonary blood flow. One of these latter patients was a young woman in the fourth month of gestation, while the other was a man who had a ventricular septal defect in addition to a ductus that was subsequently divided and ligated surgically.

Intermediate increases in pulmonary blood flow were observed in 4 patients with uncomplicated atrial septal defects. This change, which averaged 21 per cent, was directly proportional to the increase in oxygen consumption and ventilation. There was no significant change in pulmonary arterial oxygen content.

Two other patients without shunts showed slight decreases in pulmonary blood flow on sitting. These changes were comparable to those reported by Donald et al.[11] for 16 patients and 2 normal subjects without shunts.

Effects of Walking on Pulmonary Hemodynamics

The changes in total pulmonary arterial flow and mean pressure for 10 patients with central shunts during grade walking are shown in figure 2. The flow was observed to increase in all cases, whereas the pressure showed

TABLE 2.—*Hemodynamic Changes with Posture and Exercise*

Patient		O_2 consumption ml./min. STP	Ventilation L./min. BTPS	O_2 removal rate vol. %	Art. O_2 sat. %	PV-PA O_2 diff. ml./L.	Q_{t_p} L./min.	Heart rate	Pulm. stroke vol. ml.	Ventilation perfusion ratio	Pulmonary arterial pressure (mm. Hg) sys.	diast.	mean	Cor. mean	Total pulm. resistance dynes-sec.-cm.$^{-5}$	Syst. pres. sys.	diast.
KS	R*	207	4.95	4.50	96.8	35	5.9	58	102	0.8	40	15	24		325	128	64
	S*					31					26	9	15			118	78
	W*	1116	20.02	6.00	99.0	62	18.0	108	167	1.1	35	15	31	40	178	174	80
SR	R	275	7.56	4.05	92.3	21	13.1	92	142	0.6	25	14	21		128	120	76
	S										14	8	10			118	78
	W	801	18.50	4.33	97.0	34	23.5	162‡	145	0.8	16	7	12	23	78	140	78
VMcC	R	259	6.65	4.28	87.8	40	6.5	64	101	1.0	35	15	24		295	104	60
	S	270	6.85	4.32	84.0	36	7.5	72	104	0.9	28	12	18			94	60
	W	811	15.40	5.75	75.0	51	15.9	100	159	1.0	40	25	30	36	181	124	70
PK	R	175	5.02	3.80	88.5	38	4.6	72	64	1.1	27	10	14		243	108	60
	S	313	8.10	4.25	91.0	40	7.8	85	92	1.0	11	1	4			106	74
	W	850	17.30	5.40	90.0	72	11.8	136	87	1.5	16	8	10	20	135	122	72
PS	R	164	4.88	3.70	98.5	21	7.8	72	108	0.6	31	12	21		215	90	44
	S	204	7.04	3.18	94.5	24	8.5	70	121	0.8	20	0	8			96	74
	W																
JH	R	255	7.05	4.05	96.0	34	7.5	96	78	0.9	27	15	22		234	100	64
	S	284	8.11	3.92		32	8.9	136	65	0.9	31	23	27			120	82
	W	730	16.24	5.03		68	10.7	148	72	1.5	48	35	46	41	306	138	90
Mean†	R	234	6.24	4.14	92.3	34	7.5	76	97	0.9	31	14	21		245	120	65
±S.D.		±42	±1.19	±0.27	+4.2	±7	+3.3	±17	±30	±0.2			±4		±75	±15	±7
Mean	W	861	17.49	5.30	90.2	57	16.0	131	126	1.2	31	18	26	32	176	140	78
±S.D.		±148	±1.82	±0.65	±10.8	±15	±5.1	±26	±43	±0.3				±10	±55	±21	±8
Diff.		+627	+11.25	+1.16	−2.1	+23	+8.5	+55	+29	+0.3				+11	−69	+20	+13
±S.E.		±77	±1.08	±.34	±5.8	±8	±3.0	±16	±26	±.2				±5	±47	±13	±5
P		<.0001	<.0001	<.001		<.006	<.006	<.0006						<.03	<.18	<.14	<.10
JG	R	422	10.90	4.22	93.4	62	6.8	55	123	1.6	23	7	13		153	108	66
	S										10	5	7			112	82
	W	1286	27.47	5.14	82	139	9.3	90	103	3.0	20	10	16	22	189	136	60
WB	R	262	8.37	3.30	85	58	4.5	88	51	1.9	120	60	80		1420	116	80
	S										118	80	100			112	82
	W	800	25.87	3.26	80	139	5.8	152	37	4.5	140	84	117	97	1336	136	88
RF	R	384	10.94	3.98	96.6	26	14.8	82	180	0.7	60	20	35		188	134	68
	S										27	17	21			136	78
	W	1323	33.31	4.50	93.5	75	17.6	123	143	1.9	56	20	36	50	227	206	74
JP	R	244	7.76	3.30	77.6	111	2.2	83	27	3.5	124	82	98		3560	124	98
	S	277	15.30	1.90	77.0	84	3.3	115	29	4.6	116	80	96			130	86
	W																
JW	R	276	7.18	4.22	92.1	39	7.1	80	89	1.0	76	40	60		675	142	60
	S	341	8.13	4.65	91.0	28	12.2	80	153	0.6	30	22	24			142	58
	W	794	21.45	4.10	91.0	72	11.0	107	102	1.9	50	34	46	82	594	188	72
NA	R	252	6.49	4.29	91.0	32	7.9	74	106	0.8	25	12	19		192	108	58
	S	299	10.04	3.29	100.	22	13.6	105	129	0.8	16	8	12			128	60
	W	800	22.54	3.92	95.	57	14.0	140	100	1.6	25	10	17	24	137	138	60
AK	R	213	6.94	3.40	85.4	75	2.8	73	38	2.5	120	60	92		2626	125	52
	S	225	6.88	3.60	80.4	68	3.3	81	41	2.1	116	60	83			106	66
	W																
DH	R	207	(Breathing O_2)		95.3	53	3.9	66	59		30	14	25		512	90	36
	S	210	(Breathing O_2)			60	3.5	74	47		25	10	17			118	56
	W																
EW	R	157	4.82	4.36	86.6	65	2.4	88	27	2.0	30	10	18		600	130	70
	S	189	4.84	4.34	90.	83	2.3	88	26	2.1	23	14	17				
	W	426	10.82	4.40	80.	102	4.2	120	35	2.6	42	34	36	37	704		

* R = Recumbent, S = Sitting, W = Walking.

† Omitting PS who was not studied during walking.

‡ T wave in precordial ECG inverted.

considerable increases in all but 4 of these patients.

Five patients with atrial septal defects provided a fairly homogeneous group for further analysis of the changes with walking. Significant increases ($p < .003$) were observed during this exercise for ventilation, oxygen consumption, oxygen removal rate, and heart rate. The increases in pulmonary vein-pulmonary artery oxygen difference, and total pulmonary blood flow were less certain due to greater variation ($p < .006$). Increments in pulmonary stroke volume and systolic pressure of the systemic circuit were not significant. Neither was the slight rise in the average of mean pulmonary arterial pressures from 21 to 32 mm. Hg nor the calculated decrease in total pulmonary arterial resistance from an average of 245 to 176 dynes-sec.-cm.$^{-5}$ significant. Thus it is apparent that under the circumstances of these observations, patients with atrial septal defects exhibit primarily an increase in pulmonary arterial flow rather than pressure during exercise in the upright posture. This is opposite to the responses reported by Swan[12] for exercise studies performed in the supine posture. Further studies will be needed to delineate the factors favoring preferential flow across a septal defect rather than through the mitral valve to account for these differences in responses to exercise in the supine position.

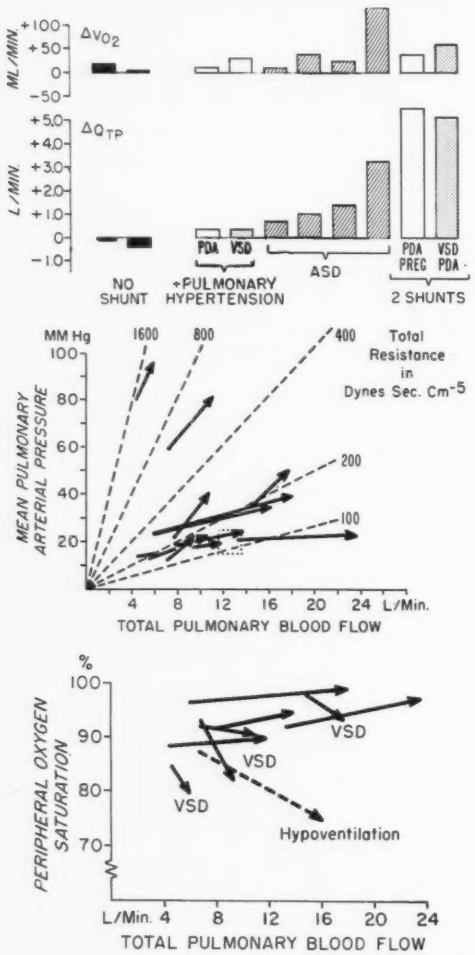

FIG. 1 *Top*. Comparative effects of changing from supine to sitting posture on oxygen consumption and total pulmonary arterial blood flow. *ASD* represents atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus and *PREG* pregnancy, in which the effects of the placenta are presumed to represent another example of shunt circulation.

FIG. 2 *Middle*. Changes in total pulmonary blood flow and mean pulmonary arterial pressure in 10 patients with central shunts. The tail of the arrow represents the values observed at rest in the supine position, and the head of the arrow indicates the values attained during the exercise of grade walking in the upright posture. The dotted square indicates the corresponding values reported by others for this level of work in normal subjects in the supine posture.[13]

FIG. 3 *Bottom*. Changes in peripheral arterial oxygen saturation, representing the magnitude of right-to-left or venoarterial shunting, as a function of changes in pulmonary blood flow with grade walking.

Changes in Arterial Oxygen Saturation with Walking

The changes in arterial oxygen saturation that occurred during walking in 10 patients with central shunts are shown in relation to changes in pulmonary blood flow in figure 3. One patient with an atrial septal defect was desaturated at rest, and markedly so with effort. Since the saturation was normal and ventilation higher when he had the initial exercise test prior to catheterization, this difference was attributed to hypoventilation secondary to depression of the respiratory center by sedation with meperidine hydro-

chloride. As a possible contributory factor, he also had clinical evidence of moderate emphysema secondary to chronic bronchitis. Three other patients exhibited a fall in arterial oxygen saturation with walking. All had ventricular septal defects. The most marked desaturation occurred in the patient with marked pulmonary hypertension, whereas the least change occurred in the patient with a small patent ductus arteriosus in addition to the ventricular septal defect. Furthermore, another patient with a large patent ductus also showed a slight fall in oxygen saturation from 92.5 to 91.0 per cent.

Discussion

From these preliminary observations, it is apparent that pulmonary hemodynamic responses in patients with circulatory shunts differ in respect to changes with upright posture and exercise from either normal subjects or cardiac patients without shunts. In contrast to the patient without a shunt, these cases show some increase in total pulmonary blood flow in the upright position. Pressure gradients across septal defects or patent ducti apparently change enough to permit greater recirculation of blood through the lungs. In patients with atrial defects this may be related to a gravitational fall in pressure in the right atrium, which is in communication with the inferior vena cava. In patients with a patent ductus, the aortic pressure may increase proportionately more than the pulmonary pressure to adjust for postural changes. Thus the redistribution of blood depends upon the complicated balances between pulmonary and systemic resistances to arterial flow and factors affecting venous return.

Inasmuch as the intrathoracic pressure was not measured, it is not possible to determine from these data whether there were any changes in true intravascular pressure in relation to changes in posture. If one assumes that the pulmonary vascular resistance was unchanged, i.e., no change in lumen size or distensibility, then there should be a change in pressure proportional to the change in blood flow. Since wedged pulmonary arterial pressures were not obtained this cannot be evaluated further.

Blood flow was calculated from the arteriovenous oxygen difference estimated from analysis of blood withdrawn from the pulmonary artery, and the assumption that oxygen saturation of pulmonary venous blood was never less than 99 per cent. If there was a diffusion defect, all the flows necessarily would be higher than reported. Furthermore, it is presumed that there is sufficient turbulence in the pulmonary artery to achieve at the point of sampling perfect mixing between systemic venous blood and shunted oxygenated blood. This may not be a valid assumption in some patients with patent ductus arteriosus.

Hemodynamic changes during both upright posture and exercise in patients with shunts indicate the magnitude of the pressure and flow work loads imposed on the heart under these circumstances. Numerous complex factors are responsible for these effects. These include the size and location of the defect, distensibility and contractile force of the heart chambers during the cardiac cycle, and resistance to flow imposed by obstructing lesions or pulmonary vascular disease. Circulatory effects of respiration and possibly changes in the volume of blood in the lungs constitute additional variables.

From these preliminary observations, a definite decrease in arterial oxygen saturation with exercise in the upright posture is more likely to be associated with a ventricular septal defect if hypoventilation or pulmonary disease can be excluded. A slight decrease can be observed with a large patent ductus arteriosus. None of the patients with uncomplicated atrial septal defects exhibited this response in the absence of inadequate alveolar ventilation. Possibly this difference may be of diagnostic value in predicting the type of shunt before definitive studies are obtained by cardiac catheterization.

Summary

Contrary to changes reported for patients without shunts, 4 patients with an uncomplicated atrial septal defect showed an average increase of 21 per cent in total pulmonary

blood flow when posture was changed from supine to sitting. The flow hardly changed in 2 patients with shunts complicated by pulmonary hypertension, whereas the flow markedly increased with this postural change in 2 other patients with either double shunts or a shunt plus pregnancy.

Total pulmonary blood flow increased in variable amounts in all patients with shunts who were studied during exercise of grade walking on a treadmill. There was a significant increase in flow in patients with uncomplicated atrial septal defects.

Pulmonary arterial pressure increased by variable amounts in all 10 patients during this exercise. The increment was not significant in 5 patients with uncomplicated atrial septal defects, but probably it was significant in patients with pulmonary hypertension at rest.

Patients with uncomplicated atrial septal defects usually maintained peripheral arterial oxygen saturation during exercise in the upright posture. One exception was a patient with mild degree of emphysema who hypoventilated, probably due to depression of the respiratory center during the study. A negligible decrease occurred in a patient with a large patent ductus arteriosus. All patients with ventricular septal defects exhibited desaturation that varied in degree with the presence of other shunts or pulmonary hypertension.

The presence of a central shunt modifies the usual circulatory adaptations to changes in posture. This difference is altered by pulmonary hypertension. Patients with uncomplicated atrial septal defects exhibit a significant increase in pulmonary flow, but not in pressure, with exercise in the upright posture. Arterial desaturation with exercise is more likely to be observed with ventricular than atrial septal defects.

Summario in Interlingua

Le presentia de un derivation central modifica le usual formas del adaptation circulatori a alterationes del postura. Iste differentias es alterate per hypertension pulmonar. Patientes con non complicate defectos atrio-septal exhibi un augmento significative del fluxo pulmonar sed non del pression quando illes es subjicite a exercitios in postura erecte. Dissaturation arterial durante exercitios es plus probabile in le presentia de defectos ventriculo-septal que in le presentia de defectos atrio-septal.

Per contrasto con le alterationes reportate in patientes sin derivation, 4 patientes con un noncomplicate defecto atrio-septal monstrava un augmento medie de 21 pro cento in le total fluxo de sanguine pulmonar quando le postura esseva alterate ab decubito dorsal a position sedente. Le fluxo esseva a pena alterate in 2 patientes con derivationes complicate per hypertension pulmonar, durante que illo accresceva marcatemente sub le effecto del mentionate alteration postural in 2 altere patientes—le un con derivation duple, le altere con derivation e pregnantia.

Le total fluxo de sanguine pulmonar accresceva a varie grados in omne patientes con derivationes qui esseva studiate durante exercitio in forma de ambulation inclinate in un machina ambulatori. Esseva notate un augmento significative del fluxo in patientes con noncomplicate defectos atrio-septal.

Le pression pulmono-arterial accresceva per varie valores in omne le 10 patientes qui executava iste exercitio. Le augmento non esseva significative in 5 patientes con noncomplicate defectos atrio-septal, sed illo esseva probabilemente significative in patientes qui habeva hypertension pulmonar in stato de reposo.

Patientes con noncomplicate defectos atrio-septal manteneva usualmente saturation oxygenic del sanguine periphero-arterial durante exercitios in postura erecte. Un exception esseva un patiente con leve grados de emphysema. Ille manifestava hypoventilation, probabilemente in consequentia de depression del centro respiratori al tempore del studio. Un grado negligibile de reduction occurreva in un patiente con grande patente ducto arteriose. Omne le patientes con defectos ventriculo-septal exhibiva dissaturation de grados variante con le presentia de altere derivationes o hypertension pulmonar.

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Gitlin, D., Craig, J. M., and Janeway, C. A.: Studies on the Nature of Fibrinoid in the Collagen Diseases. Am. J. Path. **33:** 55 (Jan.–Feb.), 1957.

Human tissues obtained at necropsy from patients with rheumatoid arthritis, disseminated lupus erythematosus, dermatomyositis, glomerulonephritis, periarteritis nodosa, and tissues obtained at operation from patients with appendicitis and placentas obtained at delivery as well as biopsied rheumatic nodules and muscle from patients with dermatomyositis, were studied to detect the presence of fibrinoid. Thin sections of the tissue were stained with rabbit antihuman fibrin antisera labeled with fluorescein. Other sections of these tissues were stained with conventional stains to detect fibrinogen and fibrin in the tissue. The fluorescent antibody method for staining to detect fibrin was much more sensitive than conventional stains. Fibrin deposited as fibrinoid was not restricted to collagen diseases, but was found in other inflammatory conditions as well. Further, the interaction of fibrin with dyes was dependent upon the medium in which the conversion of fibrinogen to fibrin occurred. This reaction is enhanced by albumin. It is considered that interstitial albumin is increased locally by the inflammatory processes, and this may be one of the parameters for the production of the dye-positive form of fibrin.

HARVEY

SPECIAL ARTICLE

Safety in Numbers

By DONALD MAINLAND, M.B., CH.B., D.SC.

THE title of this paper is mysterious, and the author's title—"statistician"—is ambiguous. The paper will, it is hoped, elucidate its own title, but regarding the title "statistician" it might be mentioned than an industrious person once recorded all the definitions of "statistics" that he could find—more than 100. What they were does not concern us here, for what we need is a definition suitable to our context, medical research. Last December I heard a definition that fitted what I had been doing in my own research and what I had been trying to show to other investigators. A number of research workers, mostly in applied biology and one or two in chemistry, were discussing the teaching of statistics to experimenters.[1] They defined experimenters' statistics as "the science and art of collecting and analyzing data in such a way as to provide valid conclusions."

Our attention is caught by 2 words, "art" and "collecting"; and we say: "Surely this is just a definition of good investigation." It might be better to call it "research methodology"; but when people receive their salaries for developing and teaching this kind of thing, and are listed on the salary sheets as "statisticians," then presumably this kind of thing is one kind of statistics. (The word "artery" originally meant "an air tube," but that does not mislead anyone in this Society today. We have become used to the changed meaning of the word.)

Experimenters' Statistics

Experimenters' statistics can be said to have been born in a brewery chemist's laboratory early in this century,[2] in the form of something that may have caught the eyes of those who read a recent report[3] on lipids and atherosclerosis. It is a bit of arithmetic called the *t* test—one of those things that are useful when we wish to know how often something that we have observed would occur if chance alone were operating.

The *t* test was taken up in agriculture and developed still further; and other tests, for other kinds of data, were developed there also.[4] In that process an important fact became obvious. If we are comparing 2 treatments, *A* and *B*, whether they are manures or drugs, it is useless to say: "Chance is very unlikely to have caused this difference in outcome," unless the only other possible cause is the thing that we are testing—the *A*-*B* difference. Factors that can cause bias, and so deceive us, can be partly eliminated by the design of the experiment, and therefore numerous very efficient experimental designs were invented[5] for use in agriculture and all other branches of science. But these designs always leave some factors, including factors that we do not know about, which may nevertheless cause bias. We must be able to say at the end of the experiment: "Either chance or the *A*-*B* difference was responsible." Therefore we must distribute the bias-causing factors by pure chance—an automatic process, nowadays usually random numbers.[6, 7]

This "randomization" is one of the basic principles of modern experimental method, and is widely used in applied sciences, including some fields related to medicine, such as pharmacologic research in the drug industry. In medicine itself, clinical experimentation,[8] an extremely difficult field, seems to have shown more progress than pure laboratory research, not only in the use of randomization, but in complex cooperative research involving well-designed plans. In 1948 appeared the classic work of the British Medical Research Council on streptomycin in pulmonary tuberculosis[9] the forerunner of other good clinical trials that

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Address given by the guest speaker at the Annual Meeting of the American Society for the Study of Arteriosclerosis, Chicago, November 11, 1956.

have been performed on both sides of the Atlantic.

Tests of "Significance"

It is not my purpose to discuss experiments at great length, but one feature should be mentioned—the analysis of figures at the end of the experiment. We can take a simple example from the streptomycin report. At the end of that experiment 4 of the 55 streptomycin-treated patients were dead, and so were 14 of the 52 controls (treated by bed rest). A mathematical test shows that if chance alone were responsible for differences in mortality, this difference would occur less than once in 50 such experiments. After a statement of this kind a feeling of uneasiness often comes to an experimenter or clinical worker. Such tests are nowadays common in medical literature, but they still look mysterious, and we are inclined to say: "How does the mathematician know what would happen in an experiment?"

I find it helpful to remember that we do not really need the mathematician's trick at all, if we are prepared to do an experiment ourselves. All that we need do is take 107 cards (one for each patient), mark 18 of them "D" (to represent the total deaths), shuffle the 107 cards very thoroughly, then count out 55 into a box labeled "Streptomycin," put the remainder into a box labeled "Controls," and record the number of "D's" in each box. By reshuffling the cards and repeating the process 1,000 times (or even 500 times) we should discover how rarely the Medical Research Council investigators' results occurred in our pure-chance experiment.

The only reason why we need to use the mathematician's trick is to save time; but actually, of course, the mathematician has produced his trick (his formula) by an experiment—an experiment on paper, and in this simple case college algebra (the binomial expansion) is sufficient to reveal that the paper experiment represents accurately what happens when chance alone is operating.

Misuse of Mathematics

Even in more complicated cases the mathematician's tricks need not worry us. Two other things should worry us much more:

1. Medical research workers often apply the tricks to unsuitable data. Before starting their investigation they should know what particular trick they are going to use, and how to conduct their investigation accordingly. But how can they do this when the mathematician, in his paper experiment, makes assumptions couched in language that few investigators understand, and when statistical "cookbooks," used by medical workers, often omit the assumptions? Moreover, the "cookbooks" rarely show how each step of an investigation connects with the final analysis, and how a false step may make this analysis misleading nonsense.

2. The second thing that should worry us greatly about statistical analysis is that in medical research we often think that a test of statistical significance is the end of the road—that something that is "significant" must be important.

In the M.R.C. streptomycin experiment, for example, there was a significantly lower mortality in the streptomycin cases than in the controls; but during the 6 months of the experiment 4 of the 55 streptomycin cases died, and the next question should be: "Taking this as a random sample of a large population of such (streptomycin-treated) patients, what do we know about the mortality in the population?" All that we can say, with a reasonable degree of confidence (95 per cent probability) is that the mortality would probably lie between 2.0 per cent and 17.6 per cent.[10] Obviously, we do not know very much about the efficacy of streptomycin as a life-saver in such patients, although the experiment showed that, in a 6-month period, it very probably delays death more than does bed rest alone.

For another example, in a group of men there may be a highly significant association between the level of a certain blood lipid and the subsequent occurrence of coronary heart disease; but if the level of this lipid is used to predict coronary disease and fails to do so in 30 per cent of the men who develop the disease, the lipid can hardly be described as a useful indicator for an individual man.

Statistics in Industry

Let us now step aside from medicine for a moment and look at industry. It is no exaggeration to say that nearly everything that we

use or consume—from light bulbs to breakfast foods, from nuts and bolts to the telephone service, and from plant fertilizers to antibiotics—has at some stage in its preparation been subjected to, or influenced by, experimenters' statistics. The new methods play a role both in production and in the testing of products.

For example, during World War II, the manufacture of a certain explosive was found to be costly and wasteful. The old-fashioned way of seeking to rectify the trouble would have been a kind of trial-and-error method, testing each of the suspected factors one at a time, while all the other factors were kept as constant as possible. Instead, an industrial statistician used a method, the factorial design, which tested all the suspected factors in the one experiment, and thereby he quickly discovered a process that increased the efficiency of production so greatly as to save many thousands of dollars. Later, the same statistician, on the staff of a pharmaceutical company, used the same method, with modifications, to discover ways of increasing the yield in penicillin production.

The factorial design has 2 advantages over the old-fashioned method:

1. It economizes time, labor, and materials. For example, we used it in an experiment to test the effects of 6 factors on radiographic bone-density readings—kilovoltage, position of films in the processing tank, speed of developing, fixation time, washing time, and drying temperature—and obtained from 128 films the information that would have necessitated, by the old-fashioned method, 8,192 films.

2. It enables one to test the effect of each factor both in the presence and in the absence of each of the other factors, all in the one experiment, and thus it creates much more of a "real life" situation than does the "one factor at a time" method.

When a product has been made, it must be tested, and that nearly always means that a sample must be taken, for measurement, chemical analysis or other tests. From the sample a prediction is made regarding the quality of the whole batch that the sample represents. If the prediction is unduly optimistic (e.g., too low an estimated percentage of defective products) the consumers' dissatisfaction will sooner or later affect the sales of the product. If, however, the prediction is unduly pessimistic (e.g., an exaggerated estimate of percentage defectives), the producer either needlessly cuts the price, or tries to find gross faults, which do not exist, in his production methods. He must, therefore, set the limits beyond which he does not wish to be in error, either overoptimistic or overpessimistic, and then he must find how large the samples must be to satisfy these conditions, where they must be taken in the batch, and at what time intervals. These are all statistical questions; and the methods used must be sound. If some industries designed their experiments as we often do in medicine, if they worshipped significance tests as we do, and if they accepted prediction values that we often accept, their more scientific competitors would very soon drive them to bankruptcy.

In medicine we can to some extent excuse ourselves by claiming that there are more difficulties, complexities, and hidden variables than in a manufacturing or agricultural process; but we must not exaggerate our claim, for any commercial process contains far more complexities, including psychologic variables, than an outsider suspects. Moreover, granting that some unique difficulties are met in human medicine, surely that is all the more reason why we should use every available method to overcome the difficulties as far as possible, and why, after many of our investigations, we should not draw "conclusions," but merely state our "impressions."

Surveys

Returning now to the prediction of coronary disease from blood lipid levels, we note that this has taken us away from experiments into another kind of investigation that is very important to us, because experimentation on human beings is often impossible. Such non-experimental research is best called a "survey"—not implying, however, that the samples must be large.

Surveys can be of various kinds; for example:

1. Attempts to evaluate a therapy by the follow-up of patients, a very difficult and often unrewarding method of therapeutic research.[11]

2. Etiologic studies, such as the search for a

relation between smoking and disease; for instance, the retrospective study of Doll and Hill[12] and the forward-going study of Hammond and Horn.[13]

Experimenters' statistics has greatly improved our survey technics. Thus, the technic of Doll and Hill might fairly be described as not very far from perfect, as a retrospective survey. Patients with lung cancer were matched against patients with other diseases by sex and age. Socioeconomic class and regional origin were well balanced. Standard forms of questions were used; and so on.

But all the characteristics, such as sex and age, for which allowance was made, are *known* characteristics, and we can hardly imagine that there are no hidden characteristics, very relevant to the problem. In 10 years we may know 1 of these characteristics, and if we made a similar survey then, we should not dream of disregarding it, any more than Doll and Hill disregarded sex and age.

After a survey, even a forward-going survey, we have always to say, in explaining the outcome: "Treatment difference, or chance, or some factor or factors unknown." Factors in a survey can be pictured as an iceberg—one ninth above the water, eight ninths below the surface. We are far too ready to think that what we see is all that matters; for it is what we do not see that may wreck our conclusions, and we have no radar equipment to detect the underwater part of our iceberg.

True, for practical purposes we may have to rest content with the results of a survey. For example, smoking is a plausible factor in the etiology of lung cancer, and we may feel impelled to advise people not to smoke; but we should never expect a survey to prove a causal relationship, and we fool ourselves if we think that a probability value, derived from testing survey data, tells us anything whatever about the hidden part of our iceberg.

Berkson's Fallacy

There are many kinds of bias that can affect surveys in medicine and in all other fields of research. An important example is the one that has been called "Berkson's fallacy," after Dr. Joseph Berkson of the Mayo Clinic who first described it in print in 1946.[14, 15] Demonstrations by simple arithmetic have been published (see Appendix); but the effect can be described without actual figures, as follows.

Let us suppose that we wish to seek a relationship between blood pressure and some feature such as age, in healthy subjects, however we may define that term. Our sample is, say, a group of industrial workers or insured persons. It is very unlikely that our sample will represent the ratios of the various age classes that exist in the general (healthy) population; and all that we now need for Berkson's fallacy to operate is that our sample shall not represent the general (healthy) population with respect to blood pressures. That is not a far-fetched notion, and, if it is correct, our conclusions will inevitably be erroneous. A spurious association between age and blood pressure may be created, or a real association may be exaggerated, or it may be hidden entirely.

We can never be sure that Berkson's fallacy is not lurking somewhere, undiscoverable, in our conclusions from a survey; but some general hints, which may help to reduce the risk, have been published.[11]

Statistical Referees

Berkson's fallacy is only one illustration of the fact that numbers—numerical data—are often far from safe; and there is in medicine a growing sense of this danger. Editors of journals, therefore, often send papers to statistical referees. But what can the referees do? Send a paper back for a statistical test? That is often the very worst thing to do. As Wilson,[16] professor of chemistry at Harvard, has said, "fifty pages of higher mathematics will not salvage an experiment with a hidden bias."

Should the referee advise the author to consult a statistician? This may help the author to improve his methods in future work; but if the statistician, after inquiring about the work reported in the paper under review, feels that he can safely analyze it, he may, quite unwittingly, be compounding a felony. For example, in the research that we conduct in our own x-ray laboratory (a strange component of a department of statistics!), we might describe, and even demonstrate, our procedure to a statis-

tician; but unless he had been in our investigation "up to his neck" throughout, we know that he might prescribe or perform a beautiful analysis that would lead to grossly erroneous conclusions. (I can vouch for this because my *alter ego*—the statistician—has blundered badly in trying to give *post facto* help to my colleagues.)

Need for Medical Biometricians

The foregoing remarks might seem to imply that in every research group on every project there should be a statistician (or biometrician), but even if that were possible it would be undesirable. Experimenters' statistics simply comprises recent developments of scientific method, and it is the research workers themselves who should know about these developments and make use of them. In applied sciences other than medicine, statisticians have found that the only way to introduce these methods properly is to go into laboratories, fields, greenhouses, and kitchens, among machinery and chemical vats. In medicine we are badly in need of people who will do the same kind of thing—people who know a great deal about the special features of medical problems.

Such people will not have a very pleasant life. They will meet criticism when they refuse to analyze figures that are brought to them, and when they decline to do anything at all with a certain project because they are already overburdened. They will meet strong resentment, because we naturally resent being shown by "an outsider" how to do things in our own field of research, and especially do we resent being shown that we are wrong, and perhaps should throw away the results of months of hard work. They will suffer more if they are junior than if they are senior. They will spend long hours on the work of others and get little kudos—hours which, if they were in any other department, they would spend on their own research, getting thereby a higher degree, higher status, and higher salary. That is a bleak picture, but if medical research workers know how bleak it is, surely they can do something to brighten it.

Attitude of Academic Medical Workers

Regarding the supply of statisticians for medical research, there is a ray of light in grants now offered by the Public Health Service to establish training programs for biometricians; but it is the opinion of some medical faculty members that such a program is inappropriate to a medical school, because the functions of a medical school, they say, are to educate physicians and to acquire new knowledge pertinent to medicine, that is, to do research.

It might be argued, of course, that the education of people to be practical experts in methodology pertinent to medical research would be an appropriate function of any medical school, because such an education must be acquired "on the job"; but the need for this new methodology is not clear to some people, especially to some laboratory workers who, in their particular work, have not seen the need. Pure biochemistry, for example, can probably be looked on as the foundation of modern medicine, and it has been enormously successful without employing modern experimental designs and analytic methods, although many of these have been developed in fields that are really applied biochemistry, such as animal feeding and pharmacologic research.

Statistics in Chemistry

The situation in biochemistry may soon change, for some biochemists appreciate fully the logic, the economy, and the beauty of the new methods; and we should remember that 10 years ago it was common to hear chemists in all fields say that statistics had no place in chemistry, whereas today the picture is very different. For example, Dr. W. J. Youden,[1] chemist and statistician at the Bureau of Standards, has visited, by invitation, nearly half of the 150 divisions of the American Chemical Society, and at some of them he has given courses of instruction on experiment design and analysis to audiences of over 200 persons. For another example, one of the best introductory guides to experimenters' statistics, for the use of laboratory workers, is a book by a Harvard professor of chemistry.[16]

The Future

Sooner or later these ideas and methods will spread throughout medicine, and perhaps the foregoing remarks will have prompted some members of this Society to consider what they might do to hasten the day when in medicine we can say: "There *is* safety in numbers—in numerical data—because we know how to collect them and how to interpret them."

Appendix

Berkson's Fallacy: Competing Admission Rates

An early demonstration of Berkson's[14] discovery occurred in a search for a possible association between diabetes and cholecystitis. There was such a strong impression of the existence of this association that some surgeons were removing gallbladders in the treatment of diabetes. To test the soundness of this belief, the prevalence of cholecystitis in diabetic patients was compared with its prevalence in persons who came to the clinic for eye testing, because it could not reasonably be suspected that there was any association between cholecystitis and errors of refraction. The frequency of cholecystitis was found to be higher in the diabetic patients by an amount that was statistically significant. Then Berkson showed that such results could be entirely fallacious.

The fallacy can affect any kind of survey of any material, living or dead, organic or inorganic. In demonstrating it we can use the symbols A, B, and X to denote 3 features, qualities, or attributes; and we can retain the hospital term "admission rate," or use the more general term "selection rate." The admission rate for, say, the attribute A is the percentage of the total population of A's that is observed in the survey. The fallacy occurs when the admission rates for A and B are different and when, also, the admission rates for X and *not*-X are different. A simple arithmetical example[17] provides the best introduction.

In a certain population are 1,000 persons with A and 1,000 with B. In each of these, 100 persons have X also. Therefore there is no closer association between B and X than there is between A and X. The admission rates to a certain survey are: for A, 50 per cent; for B, 20 per cent; for X, 40 per cent. (In this simple case, the *not*-X's have no admission rate of their own.) To find how many persons with each attribute will come into the survey, we proceed as follows:

Group A, X. Total persons = 100. Fifty per cent of them, i.e., 50 persons, are admitted because they have attribute A, leaving 50 outside. Of these latter, 40 per cent (20 persons) will be admitted because they have attribute X. Total admissions = 70. (The same result is obtained if 40 per cent of 100 are admitted first because they have attribute X, and then, from the remaining 60, 50 per cent are admitted because they have attribute A.)

Group A, *not*-X. Total persons = 900, of whom 450 are admitted because they have attribute A.

Group B, X. Total persons = 100, of whom 20 are admitted because they have attribute B, leaving 80 outside. Of these latter, 40 per cent (32 persons) are admitted because they have attribute X. Total admissions = 52.

Group B, *not*-X. Total persons = 900, of whom 180 are admitted because they have attribute B.

In summary, the following persons will be found:

	X	*not*-X	Total
A	70	450	520
B	52	180	232
Total	122	630	752

The percentage frequencies of X are as follows: Of the A's, $70 \times 100/520 = 13.46$ per cent have attribute X. Of the B's, $52 \times 100/232 = 22.41$ per cent have attribute X.

The difference (8.95 per cent) is very significant, for chance would cause such a difference less than once in 300 experiments. Something more than chance was operating, but it was not a closer association between X and B than between X and A. It was the difference in admission rates—a kind of competition between rates—and an easy way to remember the effect is by a metaphor: the higher rate for A (as compared with B) seems to have pushed the X's into the B group.

When more than 2 attributes (e.g., A, B, C, etc.) are studied, the effects are more difficult to visualize, but the mechanism is the same..

To effect a transition from attributes to measurements (e.g., age and blood pressure) it is best to begin with arbitrary classes, such as younger and older men, lower and higher pressures. In the example mentioned in the body of this paper, if younger men had a higher admission rate than older men, the younger men would be A's, the older men B's. Moderate pressure, if it had a greater admission rate than higher pressure, would be X. The competition between rates would, as it were, push the moderate-pressure men into the older age group, and this could mask, partly or wholly, a real rise of pressure with age. A similar, but more complex, picture can be conceived when measurements are arranged in numerous narrow classes, as in an actual correlation study.

Further discussion of this fallacy can be found in Berkson's second article[15] (smoking and disease; tuberculosis inferred, from an autopsy study, to be a preventive of cancer). It has been shown how the fallacy could vitiate clinicians' inferences regarding the frequency of subcutaneous nodules in rheumatoid arthritis,[11] clinical surveys,[18] anatomic, physiologic, and blood group surveys,[19] and studies of aging.[20]

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Armitage, A. K., Burn, J. H., and Gunning, A. J.: Ventricular Fibrillation and Ion Transport. Circulation Research **5:** 98 (Jan.) 1957.

Ventricular fibrillation has been studied by driving the ventricles of the isolated rabbit heart electrically and observing whether fibrillation persisted after stimulation was stopped. When the heart was perfused with a solution containing only 25 per cent of the normal content of potassium ions, it soon passed into fibrillation which could be arrested by the addition of potassium ions or adenosine triphosphate, but prolonged by dinitrophenol. The results support the theory that fibrillation depends on disturbances of the metabolic processes concerned with ion movements. It is proposed that fibrillation is due to passage of potassium ions out of the cell, which is reversed by perfusing with additional potassium ions.

AVIADO

CLINICAL CONFERENCE

EDITOR: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

Symposium on Diagnostic Methods in the Study of Left-to-Right Shunts

By ROBERT P. GRANT, M.D., RICHARD J. SANDERS, M.D., ANDREW G. MORROW, M.D., F.A.C.S., AND EUGENE BRAUNWALD, M.D.

DR. ROBERT P. GRANT: This afternoon's conference is concerned with precise methods for identifying and studying intracardiac and extracardiac shunts, both congenital and acquired. Classically, such shunts are divided into 2 types: the predominantly right-to-left shunt, which is usually associated with cyanosis, and the predominantly left-to-right shunt, which is unassociated with cyanosis. We are going to concentrate primarily on the problems of left-to-right shunts in this conference for 3 reasons: (1) they are more common than right-to-left shunts, including most cases of patent ductus arteriosus, aortic-pulmonary window, uncomplicated ventricular septal defect, ruptured aneurysm of the sinus of Valsalva, atrial septal defect, various types of atrioventricularis communis, and anomalous pulmonary venous return; (2) left-to-right shunts are more difficult to differentiate clinically from many of the more commonplace types of acquired heart diseases because the patient has no cyanosis, and specialized methods of study are often needed for this differentiation; (3) the development of a safe and convenient technic for left heart catheterization, a field in which Dr. Morrow, Chief of the Clinic of Surgery of the National Heart Institute, has given considerable leadership, has resulted in additional new technics for the study of left-to-right shunts. The studies we shall report were done largely on patients on Dr. Morrow's service and with the capable assistance of his staff.

We shall discuss 4 methods for studying intracardiac shunts that have had particular attention here: electrocardiography, blood-gas analysis, contrast radiography, and dye-dilution methods. They will be presented more or less in the order that one might use them in the study of the patient in whom a shunt is suspected. Since one of the first clues to the presence of an intracardiac shunt is often encountered in the electrocardiogram we will first discuss certain electrocardiographic features of this type of heart disease.

At the outset it must be pointed out that the electrocardiogram is a record of myocardial electric events and not of hemodynamic events. In the case of shunts it records the hypertrophy, dilatation, or other structural changes that take place in the myocardium as a result of a shunt, but it does not record the presence of a shunt itself and to this extent it can be suggestive but never diagnostic of a particular shunt. This, incidentally, is one of the principal shortcomings of the "overload" method of cataloging the electrocardiogram in congenital heart disease introduced by Cabrera and Monroy and the Mexican school,[1] for the terms "systolic overload" or "diastolic overload" are hemodynamic, and their use implies that the electrocardiogram is recording a hemodynamic abnormality, which, it can be easily proved, is not the case.

With left-to-right shunts at the atrial or, occasionally, at the ventricular level, the increased flow through the right ventricle results in right ventricular dilatation. The differentiation of right ventricular dilatation from right ventricular hypertrophy is therefore important in identifying this type of shunt, and I should like to discuss certain electrocardiographic aspects of this differentiation.

Presented by the Staff of the National Heart Institute at the Quarterly Staff Conference of the National Institutes of Health, Bethesda, Md., April 26, 1957.

Three different electrocardiographic patterns may be seen among patients with right ventricular enlargement: (1) In some patients the QRS forces generated during the first .04 second of the QRS interval are caused to point abnormally anteriorly, producing the pattern of an abnormally tall and broad initial R wave at V_1; (2) in others, the QRS forces generated late during the QRS interval are caused to point abnormally anteriorly or rightward, producing the pattern of an S wave in lead I and R′ in V_1; (3) in still others, all components of the QRS interval are weighted rightward and anteriorly; the transitional QRS complex in the precordial leads shifts to the right and the mean QRS axis deviates rightward.

The reason for the 3 different patterns is related to the sequence in which the various regions of the right ventricle are activated during the QRS interval, as has been elucidated by the study of right ventricular conduction defects. In conventional human right bundle-branch block the electric forces generated during the first .04 second of the QRS interval are not altered by the conduction defect. There are many reasons for believing that the first .04 second of the QRS interval is spared because the site of the block lies far out along the right ventricular conduction pathway, in the free wall of the right ventricle.[2] If this is true, the septal portion of the right ventricle contributes its electric forces during the first .04 second of the QRS interval; only when the septal and paraseptal portions of the right ventricle are involved in the hypertrophy will abnormal right ventricular forces be evident in the first part of the QRS complex (the first pattern described above). The free wall of the right ventricle contributes its electric forces during the second half of the QRS interval. One can conjecture that when the inflow region of the free wall of the right ventricle (the portion that rests on the diaphragm) is predominantly hypertrophied or dilated, the terminal QRS forces will point inferiorly and right axis deviation will be the result (the third pattern mentioned above); if the outflow portion and crista regions of the free wall are principally involved, the terminal forces will point anteriorly and rightward, and an R′ will be written at V_1 (the second pattern mentioned earlier).

This hypothesis helps to explain some of the QRS patterns encountered in congenital heart disease. Figure 1 contrasts the electrocardiographic findings before and after surgery in atrial septal defect, an example of right ventricular dilatation, with the electrocardiographic findings in uncomplicated pulmonic stenosis, an example of right ventricular hypertrophy. Let us look first at the tracings of the atrial septal defect. The QRS interval is slightly prolonged, measuring .10 second with rightward and somewhat anteriorly directed terminal forces suggesting a right ventricular conduction defect. However, the terminal forces are not generated until after the first .03 second or more of the QRS interval has elapsed, indicating that the conduction defect must lie in the free wall of the right ventricle. Also the first .03 second of the QRS complexes in the various leads is not particularly abnormal in direction. For example, at V_1 there is a tiny R followed by the beginning of an S wave resembling that seen in the normal QRS complex at V_1. Nor is there much change in the initial QRS forces following closure of the defect—note how similar the initial limb of the QRS loop is before and after surgery. The chief effect has been a reduction in the magnitude of the rightward forces generated later during the QRS interval. According to the theory under discussion these findings suggest that the septal portion of the right ventricle is not greatly involved in the architectural changes of the right ventricle in atrial septal defect. This agrees with the pathologic findings, for the often enormous dilatation of the right ventricle in atrial septal defect is nearly entirely at the expense of the free wall, with little involvement of the septum.[3]

In contrast, let us now look at the tracings in the case of pulmonic stenosis. In the preoperative tracing there is no QRS-interval prolongation, and conduction defects of the usual type are uncommon in this disorder. But, of greater importance, the abnormal rightward and anteriorly directed forces appear much earlier during the QRS cycle than they did in the case of atrial septal defect. From our theory, this must mean that the septal region of the right ventricle is involved to an important extent by the hypertrophy; and this of course agrees with the findings of the pathol-

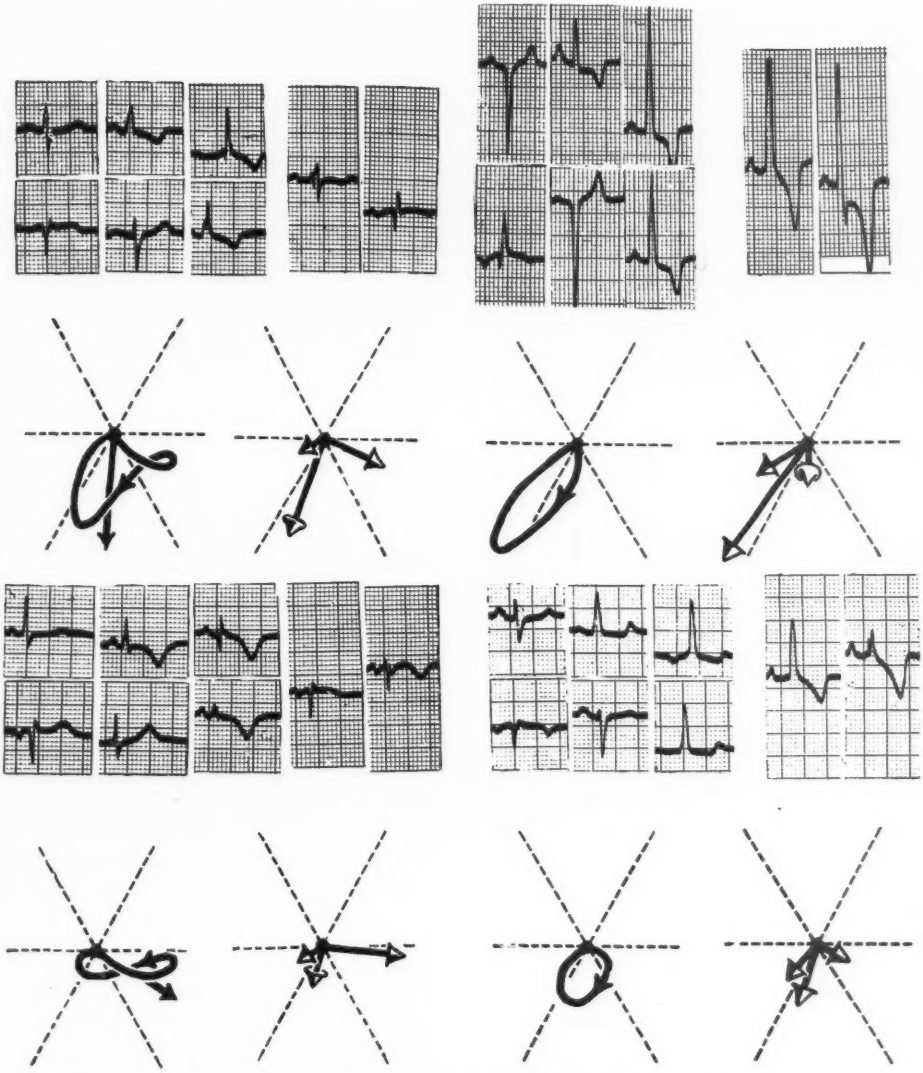

FIG. 1. *Left*, 37-year-old patient with atrial septal defect before (*above*) and 9 months after (*below*) surgery. *Right*, 12-year-old patient with uncomplicated pulmonic stenosis before (*above*) and 11 months after (*below*) surgery. Limb leads on the left of each tracing, with standard leads above the unipolar leads below; V_1 and V_2 on the right for each tracing. QRS loop, mean QRS axis, and 3 instantaneous spatial QRS vectors were calculated from the conventional tracings.

ogists. Following successful valvulotomy both the initial septal forces and the later free wall forces become more normal as the hypertrophy subsides. In summary, it is suggested that in general the RSR′ pattern at V_1, seen most characteristically in atrial septal defect, is a consequence of marked dilatation of the free wall of the right ventricle with sparing of its septal region, while the simple tall R-wave pattern seen classically in pulmonic stenosis is due to concentric right ventricular hypertrophy. Of course this is not a hard and fast rule and there are gradations between the 2 patterns, but it may serve as a useful starting point for critical and enlightening correlations of the electrocardiogram with various forms

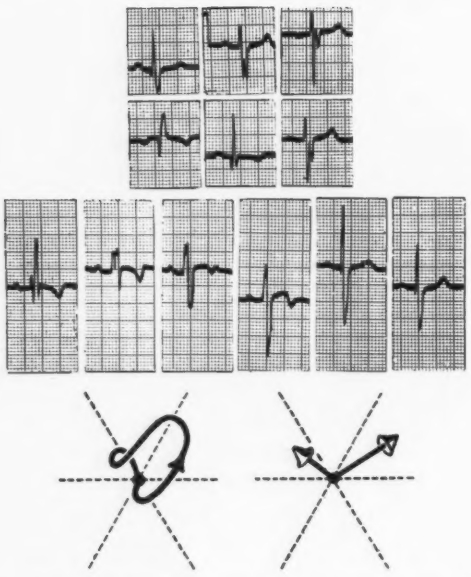

FIG. 2. Sixteen-year-old patient with surgically proved persistent ostium primum atrial septal defect. Limb leads above, with standard limb leads and unipolar limb leads; V_1 to V_6 leads below. QRS loop and spatial vector for first .04 second and for last .04 second were plotted from the conventional tracing.

and etiologies of right ventricular hypertrophy and dilatation.

The tracings I have shown you of atrial septal defect and of pulmonic stenosis are typical but not necessarily diagnostic of the 2 lesions. Slight QRS prolongation with abnormal right ventricular forces late in the course of the QRS cycle (often called the RSR pattern, after the contour this produces at V_1) is seen in the majority of cases of atrial septal defect of the secundum type. But it is also seen in a small percentage of patients with ventricular septal defect and in 20 per cent of patients with mitral stenosis. It is characteristic of disorders associated with marked right ventricular dilatation; atrial septal defect and anomalous pulmonary venous return are the commonest causes. It is interesting that greater degrees of QRS prolongation (to .12 second or more) with this type of terminal QRS pattern (i.e., right bundle-branch block) occur no more commonly in atrial septal defect than in ventricular septal defect or mitral stenosis. This is another cogent reason for believing that the conduction defect in atrial septal defect is not simply "incomplete right bundle-branch block" but rather some sort of parietal block, perhaps due to the fibrosis that accompanies marked dilatation. Some workers have attributed the QRS prolongation to right ventricular hypertrophy per se. This seems to me an unlikely explanation, since prolongation is so uncommon in pulmonic stenosis where the severest hypertrophy may be encountered.

The QRS alteration in the persistent ostium primum type of atrial septal defect is quite different from that seen in the ostium secundum type that we have been discussing; the differentiation of the 2 types of atrial septal defect is of great importance to the surgeon. The electrocardiogram of a patient with persistent ostium primum is shown in figure 2. There is marked left axis deviation of the first .04 second of the QRS interval followed by a right ventricular conduction defect. The mean vector for the first .04 second of the QRS interval must be markedly leftward, more than −30 degrees, in order to make the diagnosis of persistent ostium primum, because the adult with an ostium secundum defect may sometimes have a horizontal initial vector. More than 80 per cent of cases of persistent ostium primum have this initial vector deformity of the QRS complex. It is seen as frequently in atrioventricularis communis, less often in truncus arteriosus and single ventricle, and a similar pattern is occasionally seen in fibroelastosis. It must not be confused with the left axis deviation seen in tricuspid atresia. In such patients there is no terminal right ventricular conduction defect and the initial vector is horizontal but not so markedly leftward in direction.

The left axis deviation of initial QRS forces in persistent ostium primum has been attributed to mitral insufficiency resulting from the mitral valve deformity that is often a part of the structural defect in these patients. I think this explanation is unlikely for 2 reasons: (1) left axis deviation is not usually seen in pure rheumatic mitral insufficiency and there is therefore no a priori reason to expect it in these cases; (2) the patient whose tracing is shown in

igure 2 was operated upon and no regurgitant et was felt in the left atrium.

QUESTION: How do you explain the fact hat certain cases of pulmonic stenosis with lectrocardiograms like the one you showed, will postoperatively go through a stage of RSR′ at V_1 resembling the tracing of an atrial eptal defect?

DR. GRANT: We have seen this, too. I imagine hat as the right ventricular hypertrophy subsides and the septal contribution returns toward normal an RS returns at V_1; I don't know whether the persistence of the terminal R′ means that the free wall returns to normal more slowly than the septal region or that there is a minor parietal block in the free wall in the pulmonic stenosis.

The next step one might well take in the study of the patient with a suspected shunt is a right heart catheterization. With this technic, left-to-right shunts are usually detected and localized by determinations of the oxygen content of blood samples from the right heart. The use of oxygen differences to detect a shunt leaves much to be desired. Several years ago Dr. James Calloway, now in Nashville but then a member of our staff here at the National Heart Institute, made experimental observations on the use of nitrous oxide (N_2O) instead of oxygen in the detection of left-to-right shunts. Dr. Sanders of the Clinic of Surgery will describe our clinical experience with the N_2O test.

DR. RICHARD J. SANDERS: The nitrous oxide test[4] is performed during right heart catheterization. After a sample of blood has been drawn for nitrogen blank determination the patient breathes a mixture of 15 per cent N_2O, 21 per cent O_2 and 64 per cent N_2 for 1 minute. During this period blood samples are drawn simultaneously from the right heart and femoral artery. These samples are then analyzed for N_2O content.

N_2O is used as the test gas because of the wide arteriovenous difference that exists during the first minute of its inhalation. N_2O is a soluble inert gas; the arterial level rises quickly while the venous level lags because of absorption by the tissues. In the presence of a left-to-right shunt left heart blood rich in N_2O increases the N_2O content of right heart blood distal to the shunt. The larger the shunt the higher will be the N_2O level in the right heart blood. Because the arterial N_2O level is variable, the N_2O content of right heart blood is expressed as a percentage of the arterial content, the N_2O ratio. On the basis of N_2O tests in over 200 patients it has been established that a left-to-right shunt is present if the N_2O ratio in the right ventricle or pulmonary artery exceeds 20 per cent or if it exceeds 30 per cent in the right atrium. The test is ordinarily performed first with pulmonary artery blood to detect or exclude the presence of any left-to-right shunt. If a shunt is found, it is localized by repetition of the test in the right ventricle and right atrium.

Large differences in the O_2 content of blood from the chambers of the right heart may be normal and even multiple samples from a single chamber may vary widely. Because of these normal variations, an O_2 stepup of at least 1.5 volumes per cent must be present in right atrial samples for the diagnosis of a left-to-right shunt at this level. The diagnosis of a shunt into the right ventricle or pulmonary artery requires an increase of at least 1.0 volume per cent. Table 1 illustrates this problem in a patient with a small patent ductus arteriosus. The O_2 contents of samples from the right heart vary by as much as 1.1 volume per cent and the difference between right ventricular and pulmonary artery blood is only 0.4 volume per cent, considerably below the diagnostic level. The N_2O ratio in this patient was 22 per cent in the pulmonary artery, diagnostic of a small shunt.

TABLE 1.—*Oxygen Content of Blood Samples and Nitrous Oxide Test in Patent Ductus Arteriosus*

O_2 Samples—PDA			
SVC	*RA*	*RV*	*PA*
12.3	13.0	14.0	14.2—L
13.4	13.8	14.6	15.2—R
	14.1	14.8	15.3—M
Average Values			
12.9	13.6	14.5	14.9

N_2O Test

$$\text{Pulmonary A.} — \frac{PA}{A} = \frac{.75}{3.42} = 22 \text{ per cent}$$

TABLE 2.—*Oxygen Content of Blood Samples and Nitrous Oxide Test in Atrial Septal Defect*

O_2 Samples—IASD

SVC	*IVC*	*RA*	*RV*	*PA*
12.8	17.8	14.4	16.7	16.9
13.6	18.1	14.5	18.3	17.1
		17.7	18.5	18.3
				18.9

Average Values

Cavae	*RA*	*RV*	*PA*
16.3	15.5	17.8	17.8

N_2O Test

Pulmonary A.—$\frac{PA}{FA} = \frac{1.87}{3.80} = 43$ per cent

Rt. Atrium $\frac{RA}{FA} = \frac{2.30}{4.00} = 57$ per cent

Another advantage of the N_2O test is that blood samples proximal to any shunt need not be drawn. In patients with suspected atrial septal defect, for example, several samples from each vena cava must be drawn for O_2 analysis in attempt to obtain a representative caval value. Certain inferior caval samples may have excessively high O_2 content because of sampling from laminar streams of renal venous blood. With the N_2O test this problem is obviated, for the vena caval contents have not been found to exceed 30 per cent of the arterial content. Therefore, a ratio of 30 per cent or more in the right atrium is diagnostic of a shunt at this level.

Table 2 shows the data obtained in a patient proved to have an atrial septal defect. The inferior caval oxygen samples, when doubly weighted and averaged with the superior caval oxygen samples, give a mixed caval value that exceeds the average atrial value. Although the single sample of 17.7 volumes per cent in the right atrium suggests a shunt, this is not conclusive because it could represent the same laminar stream sampled in the inferior cava. However, the N_2O tests in this patient make the diagnosis clear. The N_2O ratio of 43 per cent in the pulmonary artery establishes the presence of a shunt and the right atrial index of 57 per cent localizes the shunt to this level.

These examples are selected from 22 patients in whom the N_2O test afforded a correct diagnosis and the O_2 method a false one. These occurred in a group of 149 patients in whom both tests were performed.

QUESTION: Nitrous oxide is an anesthetic agent. Does the patient experience any symptoms during the test?

DR. SANDERS: We use such low concentrations of N_2O that there are no apparent anesthetic effects. The patient breathes it for only 1 minute and most of the N_2O is eliminated within 5 minutes. To be safe, we usually wait 10 minutes before repeating the test in another chamber of the heart, but 5 minutes are probably sufficient.

QUESTION: How rapidly can determinations of N_2O content be made, and does the patient breathe at his normal rate or do you have him hyperventilate the N_2O?

DR. SANDERS: The manometric determination takes from 10 to 15 minutes. After the test in the pulmonary artery has been done, the samples are immediately analyzed. If the test is positive, or even suggestive, it is repeated in the right ventricle and right atrium. To answer the second question, the patient hyperventilates during N_2O inhalation to get a high arterial level as rapidly as possible. This gives us a larger arteriovenous difference during the first minute.

DR. ANDREW G. MORROW: I'd like to make one comment. Dr. Sanders has progressed farther with this line of work than he has told you. Indeed, I think that in our laboratory we may in time abandon oxygen determinations altogether in our diagnostic catheterization work. With the proper equations one can calculate the magnitudes of shunts from N_2O data. Dr. Sanders is now experimenting with radioactive inert gases. With these, the samples can be assayed almost instantly by simply dropping the syringe into a scintillation counter and the results are available in a matter of seconds.

DR. GRANT: The presence of a shunt having been demonstrated, it now becomes important to the surgeon to know the detailed anatomy of the defect. For this purpose contrast roentgenographic technics are often used, and Dr. Morrow is going to tell you of his experiences with aortography and left ventriculography.

DR. MORROW: The injection of contrast substances into the chambers of the heart and the great vessels is another useful method for

studying left-to-right shunts. To date we have done more than 100 such selective contrast studies at the National Heart Institute. I should like at this time to acknowledge the assistance we received in this work from Dr. Hans Eric Hanson, of Stockholm, who was a visiting scientist with us last year; of course, we also had the fullest cooperation from Dr. Hilbish and his staff in the Department of Radiology of the Clinical Center.

Aortography and left ventriculography are potentially dangerous procedures. Thus far, however, we have not had any deaths or serious sequelae from them. Before discussing the usefulness of these studies I should like to spend a few moments describing the technic itself. A small incision is made in the right forearm just below the antecubital crease. The brachial artery and its radial and ulnar branches are dissected free, and as large a catheter as possible is passed through one of the branches, usually the radial. I emphasize the importance of exposing both branches, so that one is certain that the incision is not made in the main brachial trunk. Under fluoroscopic control the catheter is advanced into the ascending aorta and its tip is positioned immediately above the aortic valve. Correct placement of the catheter tip is probably the single most important aspect of the procedure. If the contrast material is injected in the ascending aorta, against the blood stream, it will be completely mixed with blood and will not reach the cerebral circulation in dangerous concentration. We do not compress the carotid arteries and thus far have not had cerebral complications. The position of the catheter tip is checked by biplane x-rays before the patient is anesthetized and before the injection is made.

The catheter is passed into position with local anesthesia only. When we are ready for the injection the patient is anesthetized with Pentothal and succinyl choline. Respiration is controlled entirely by the anesthetist. Immediately before the injection is made the patient is hyperventilated with 100 per cent oxygen for 30 or 40 seconds. At the time of the injection full inspiration is held by constant pressure on the bag. This maneuver not only provides oxygenation but also the positive pressure during the injection slows blood flow and consequently there is slower passage of the sodium acetrizoate (Urokon). The usual dose of 70 per cent Urokon is 1 ml. per Kg. of body weight. We have seldom, however, exceeded 70 ml. of the 70 per cent solution. The injection is made with a Gidlund syringe with a pressure of 10 Kg. per cm.^{2} (144 lb. per sq. in.). With this device we can inject 50 ml. of 70 per cent Urokon through a no. 9 catheter in about 1 second. Biplane x-rays are taken at the rate of 4 or 6 per second. After the study has been completed, the catheter is withdrawn and the arteriotomy wound is carefully repaired. In virtually all patients the pulse in the distal artery returns immediately. We have made it a practice never to repeat an injection until at least 30 days have elapsed.

Now for some examples of the clinical usefulness of this procedure. The first patient is the one described by Dr. Sanders—a young woman with a very faint continuous murmur over the precordium and in whom no left-to-right shunt could be detected by oxygen differences. The aortogram revealed (fig. 3) a patent ductus arteriosus scarcely 3 mm. in diameter.

Ordinarily the diagnosis of patent ductus is not difficult. However, a frequent diagnostic

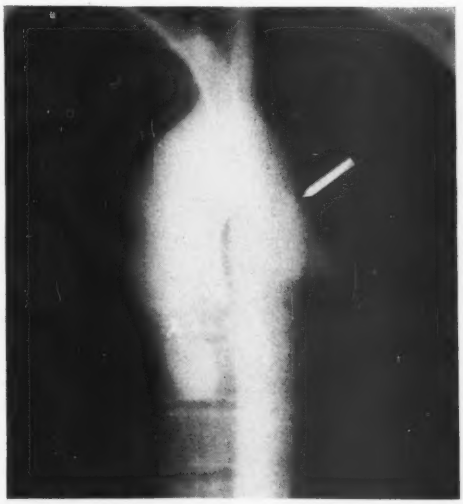

FIG. 3. Anteroposterior film showing slight opacification of the pulmonary artery and a small patent ductus, indicated by the arrow. In this view the ductus is seen end-on.

problem is whether the patient has a patent ductus or another type of aortic-right heart communication. One of these is aorticopulmonary window, a communication between the aorta and pulmonary artery at the base of the heart. This problem was presented in a child of 14. Right heart catheterization revealed a large oxygen difference between the right ventricle and pulmonary artery. His murmur was atypical, however, and for various other reasons it was considered that he might not have a patent ductus. His aortogram is shown in figure 4. The diagnosis of aorticopulmonary window was established by the appearance of the contrast material in the pulmonary artery before the aortic arch was opacified. This defect was divided and closed successfully with the aid of general hypothermia.

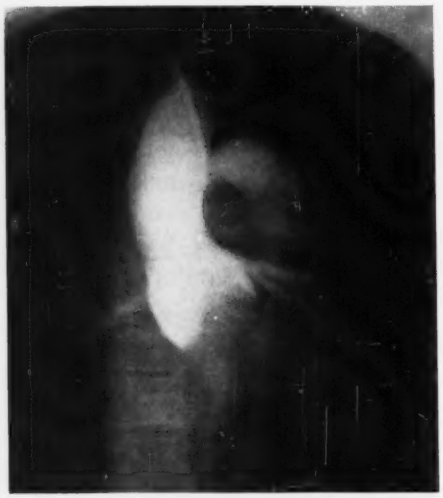

FIG. 4. Aorticopulmonary window. Dye is seen in the main pulmonary artery before it has passed the transverse aortic arch.

Similar differential diagnostic points were considered in another patient. He was a healthy young man who suddenly went into heart failure and presented a loud continuous murmur over the precordium. Because of the sudden onset of his disease, ruptured aneurysm of the sinus of Valsalva was considered to be a likely diagnostic possibility. His aortogram is shown (fig. 5). A jet passes from the base of a deformed and perforated right coronary sinus into the right atrium. This aneurysm was closed by means of a plastic sponge prosthesis.

The fourth patient presented a somewhat similar problem. He also had a continuous murmur over the anterior chest but had no

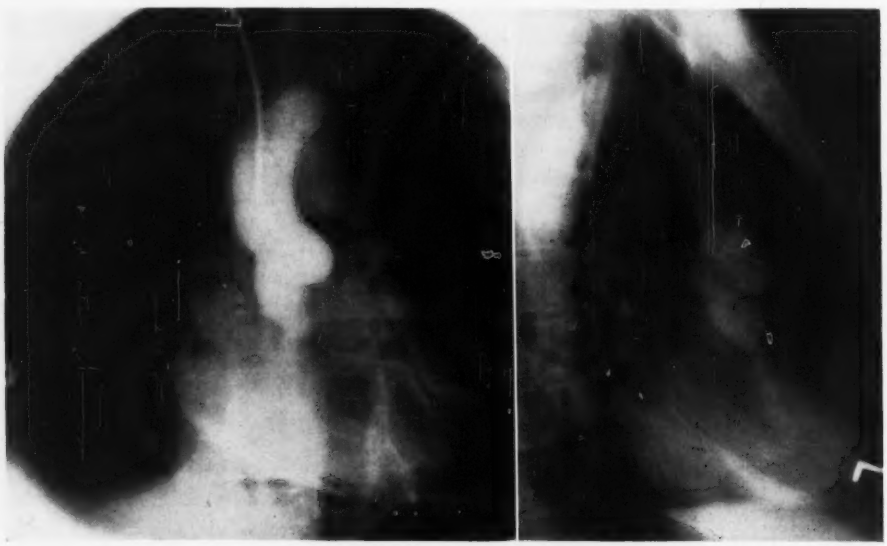

FIG. 5. Anteroposterior and lateral views showing rupture of an aneurysm of the sinus of Valsalva into the right atrium. The right coronary sinus is deformed and a jet passes into the atrium immediately proximal to the tricuspid valve.

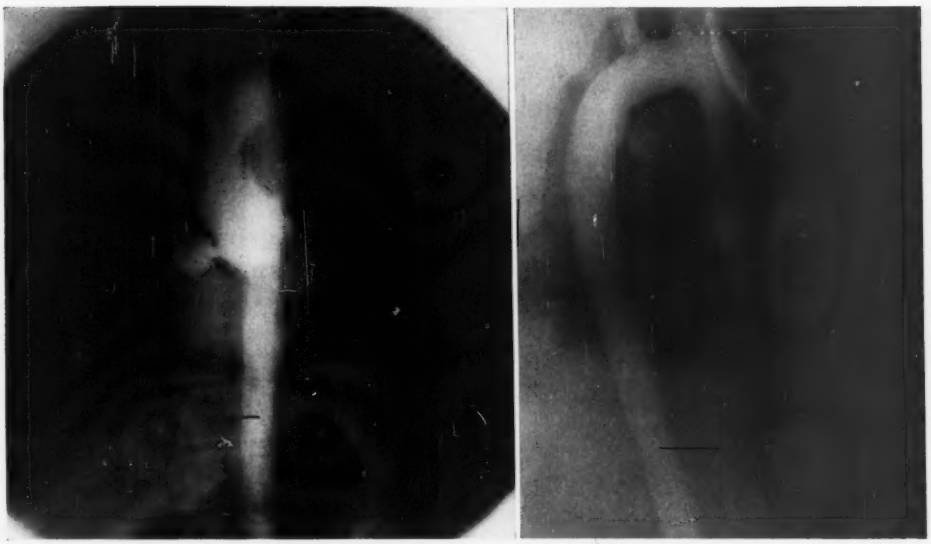

FIG. 6. Anteroposterior and lateral views illustrating a fistula between a branch of the right coronary artery and the right atrium. The right coronary sinus is dilated but not ruptured. A normal branch of the right coronary artery arises anteriorly and a dilated and tortuous branch enters the right atrium posteriorly.

symptoms and no history of heart failure. A small shunt into the right atrium was detected at right heart catheterization. The aortogram is shown in figure 6. There is a dilated and tortuous branch of the right coronary artery entering the right atrium. At operation, utilizing extracorporeal circulation, the absence of a ruptured sinus aneurysm was confirmed when the aorta was opened. The fistula was then successfully closed from the right atrium.

Another young man also presented with a continuous murmur over the base of the heart somewhat to the right of the sternum. He had bounding pulses and was referred with the diagnosis of ruptured sinus aneurysm. There was no evidence of any left-to-right shunt at catheterization. His aortogram (fig. 7) showed a bicuspid aortic valve with aortic insufficiency. He had enough valvular deformity to cause a continuous murmur. There was no communication with the right heart.

Dr. Grant has mentioned the necessity of differentiating the ostium secundum atrial septal defect from persistent ostium primum and other varieties of common A-V canal. The ostium secundum type is readily amenable to closure under direct vision with hypothermia. The operation is relatively safe and the results are good. The ostium primum type of defect requires extracorporeal circulation and the technic of closure is considerably different. This differentiation was necessary in a boy of 14 with a large left-to-right shunt at the atrial level. His electrocardiogram, which I will not describe, made Dr. Grant suspicious of an ostium primum defect. A left ventriculogram was performed. The catheter was passed along the brachial artery into the aorta, but instead of leaving it in the root of the aorta it was manipulated through the valve so that its tip lay in the outflow tract of the left ventricle. The films are shown in figure 8. Urokon passed from the left ventricle through an incompetent mitral valve into the left atrium and across the atrial defect. This was thought to be an incomplete type of common A-V canal with a cleft mitral valve but without a ventricular septal defect. At operation this diagnosis was confirmed; the cleft valve was repaired and the atrial defect closed while the patient was maintained by extracorporeal circulation.

QUESTION: Do you worry about Urokon in the coronary arteries?

DR. MORROW: Not at all. You have probably

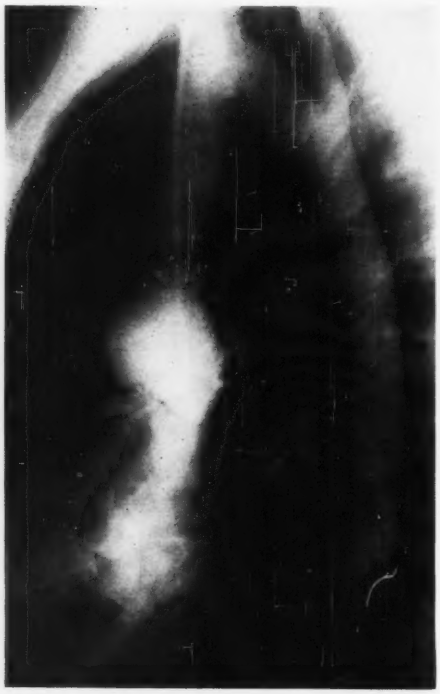

FIG. 7. Aortic valve deformity with aortic insufficiency that was responsible for a continuous murmur. Only 2 sinuses of Valsalva are visible and there is regurgitation from the aorta into the left ventricle. The injection does not produce regurgitation when made above a normal valve.

noticed in the films that we usually get good coronary filling. This technic has not been fully exploited in the study of patients with coronary artery disease. There are usually no electrocardiographic changes with the injection.

DR. GRANT: There is another technic for studying left-to-right shunts that is similar to this but much simpler and probably safer. This is the dye-dilution method with left heart injection. Dr. Braunwald will tell you about this method.

DR. EUGENE BRAUNWALD: Dr. H. L. Tanenbaum, Dr. Morrow, and I have been interested in a technic involving indicator-dilution curves for the detection and precise localization of left-to-right shunts. This technic consists of injecting an indicator dye into the catheterized left heart or aorta and obtaining dye-dilution curves either from the femoral artery with a continuously recording densitometer[5] or from the heat-flushed ear with a Wood oximeter.[6] In patients without shunts, the injection of indicator dye into a pulmonary vein, left atrium, left ventricle, or thoracic aorta yields a dilution curve with a smooth rapid ascent and descent. In contrast, when the injection is made proximal to the origin of a left-to-right shunt, a fraction of the indicator passes through the pulmonary circulation and interrupts the smooth, rapidly descending limb of the primary curve, giving it a secondary peak or an abrupt change in its rate of fall. We have used this technic in 85 patients[7, 8] and in a group of dogs in which Dr. R. R. Baker had produced left-to-right shunts,[9] and have found it to be a very satisfactory method for making an accurate differential diagnosis between various types of left-to-right shunts. Its applications in 2 patients who presented difficult diagnostic problems will be discussed.

A 46-year-old male had predominantly right heart failure. The findings on physical examination, electrocardiogram, and x-ray were compatible with the diagnosis of an atrial septal defect. At right heart catheterization the pulmonary artery pressure was 39/15 mm. Hg and the N_2O test indicated a left-to-right shunt at the atrial level. The catheter could not be manipulated into the left atrium but repeatedly passed from right atrium into a right superior pulmonary vein. In order to determine whether or not there was an atrial septal defect in addition to the anomalous pulmonary vein, transbronchial left heart catheterization[10] was carried out. Following the injection of indigocarmine into the left atrium a normal dilution curve was obtained from the femoral artery (fig. 9). The presence of a left-to-right shunt in the left atrium, left ventricle, or aorta was thereby excluded, and the presumptive diagnosis of isolated anomalous pulmonary venous drainage was confirmed. If an associated atrial septal defect had been present, a portion of the dye injected into the left atrium would have been shunted across into the right atrium and modified the descending limb of the dilution curve.

The second patient was an 18-month-old child who presented clinical evidence of a left-

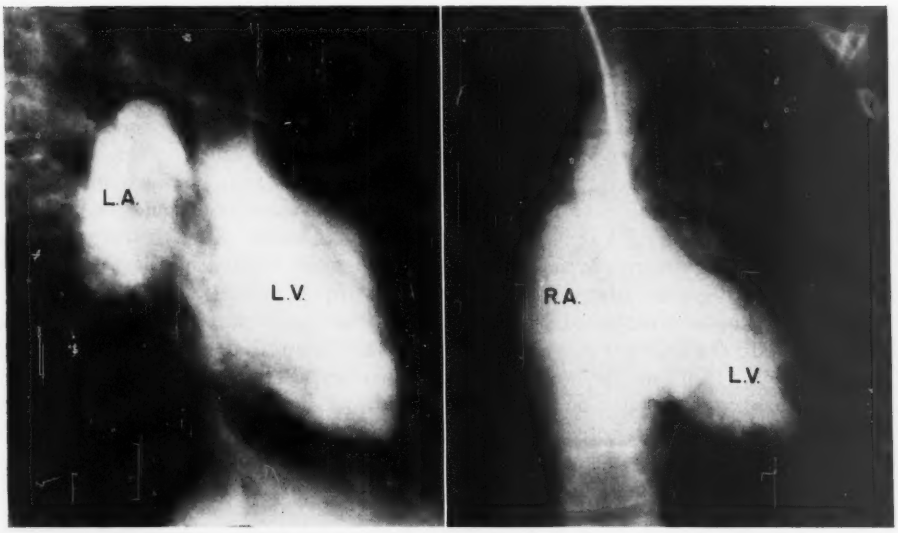

FIG. 8. Ostium primum atrial septal defect with mitral insufficiency. The injection was made into the left ventricle. In the early lateral view (*left*) the left atrium opacifies from the ventricle. Shortly thereafter the anteroposterior view (*right*) shows filling of the right atrium from the left atrium. At operation the mitral valve was found to be cleft.

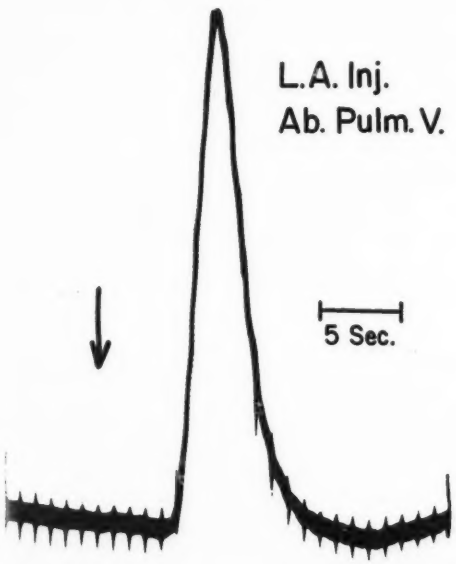

FIG. 9. Dye-dilution curve following left atrial injection in a patient with partial anomalous pulmonary venous drainage. Normal contour rules out the presence of an associated atrial septal defect. Vertical arrow indicates midpoint of injection.

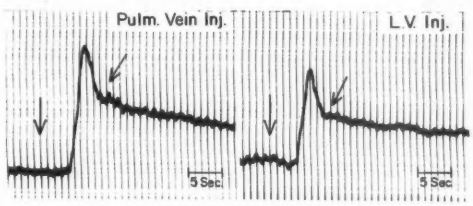

FIG. 10. Dye-dilution curves in a patient with an atrioventricular canal. After left ventricular injection the descending limb of the dye curve was interrupted by an abrupt change in the rate of fall in concentration (*oblique arrow*), indicating that left ventricular blood was shunted from left-to-right and through the pulmonary circulation. The contour and time of appearance of dye after pulmonary vein injection are identical.

to-right intracardiac shunt and pulmonary hypertension. At right heart catheterization the nitrous oxide index in the right atrium was 36 per cent, indicating the presence of a left-to-right shunt at the atrial level. The catheter was manipulated across the atrial septum into the left atrium, and was advanced into the left ventricle. Dye was then injected into the left

ventricle in order to determine whether a simple atrial septal defect was present or whether the anomaly fell into the class of common atrioventricular canal. In this latter anomaly blood from the left ventricle would be shunted into the rghit heart and pulmonary circulation, either across a ventricular septal defect or through an incompetent mitral valve into the left atrium and then into the right atrium. The dye curve following left ventricular injection was abnormal (fig. 10), indicating that left ventricular blood was shunted from left-to-right, thus excluding the presence of a simple atrial septal defect. The catheter was then manipulated into a right superior pulmonary vein and indigo-carmine was injected into it. The resulting dye curve (fig. 10) resembled that following left ventricular injection both in contour and in the short appearance time of the dye (4.0 seconds). This result indicated that the pulmonary vein in question drained into the left atrium. Upon injection into a pulmonary vein with anomalous drainage the appearance time was markedly prolonged, since dye must pass through the right heart and pulmonary circulation before it reaches the left heart. The contour of the curve was also modified in that the ascending limb and early descending limb were not as steep as when the injection was made into a vein that drains into the left atrium.

Dye-dilution curves resulting from aortic injections have also been found to be helpful in the differential diagnosis of left-to-right shunts at the base of the heart.[8] When the shunt originates just distal to the aortic valve, as in aortic septal defect or in ruptured aneurysm of the sinus of Valsalva, dye curves following injections into the ascending aorta just above the aortic valves are abnormal. However, when the injection is made into the aortic arch at the origin of the left subclavian artery, a normal curve results. On the other hand, in the presence of a patent ductus arteriosus dye injection into the aorta at the level of the left subclavian artery will yield an abnormal curve with evidence of a left-to-right shunt.

QUESTION: Can you quantify the shunt by this method?

DR. BRAUNWALD: We have not made any attempts to measure the volume of the shunt from the curves. In order to treat the curves quantitatively it would have to be assumed that the dye is instantaneously and completely mixed with the blood.

QUESTION: Does mitral or aortic insufficiency give you an abnormal curve?

DR. BRAUNWALD: We have studied over 20 cases with valvular insufficiency. When the injection is made into the left ventricle in patients with mitral insufficiency or at the root of the aorta in patients with aortic insufficiency, a characteristic curve results that is quite different from the one produced by left-to-right shunts. The ascending limb is steep and rapid and the descending limb is abnormally prolonged and slow but shows no sudden breaks. This contour probably is the result of repeated regurgitation of portions of the dye.

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CLINICAL PROGRESS

Interference Dissociation

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INTERFERENCE dissociation is one of the most interesting arrhythmias. Although formerly considered a rarity,[1] it is now recognized to be quite common; Katz and Pick,[2] for example, found the surprisingly high incidence of 681 instances in a series of 50,000 consecutive patients. No doubt many cases escape detection simply because dissociation due to interference is usually transient, and by chance may not be recorded in a routine short tracing. However, all too frequently this arrhythmia is misdiagnosed, even by experienced electrocardiologists.

In the past, interference dissociation attracted little attention in clinical practice because it is essentially a benign disorder, insidious in onset, almost entirely asymptomatic, and of no great diagnostic or prognostic importance. In recent years, however, there has been a revival of interest in the arrhythmias in general, stimulated by advances in cardiovascular surgery and related fields. The complete electrocardiologist of today must be prepared to interpret correctly the most difficult arrhythmias, including all the complex variations of interference dissociation. For this reason we thought it would be timely to present a comprehensive as well as a detailed description of the electrocardiographic manifestations of interference dissociation.

MATERIALS AND METHODS

Electrocardiograms obtained from 12 cases have been selected for analysis. These patients were observed either at the East Orange Veterans Administration Hospital, the Cardiac Clinic of the Newark Health Department, or in private practice. In some of the figures the cardiac mechanism is illustrated diagrammatically. The customary conventions are employed to indicate atrial and ventricular systole and atrioventricular conduction. The horizontal line through the atrioventricular (A-V) space indicates the level of the A-V nodal pacemaker, but no attempt is made to locate this position accurately. When P waves cannot be clearly seen because of superimposition upon QRS complexes, their position is set arbitrarily and related time intervals are roughly estimated. The unavoidable errors in timing that are thereby incurred are probably not significant. Time intervals are in hundredths of a second. P-R and R-P intervals are recorded when present.

The following discussion is based upon analysis of these electrocardiograms, experience with a large number of additional cases of interference dissociation and a review of the pertinent literature.

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NOMENCLATURE

In consulting the literature one is soon impressed by the obvious fact that there is no unanimity of usage of terms with reference to A-V nodal rhythm, A-V block, interference, A-V dissociation, interference dissociation and related phenomena. Standardization of the nomenclature for these arrhythmias is to be hoped for in the future. Meanwhile, the terminology adopted for our present purposes will be clarified when indicated.

A-V NODAL RHYTHM

The term A-V nodal rhythm in general usage implies that the A-V node controls both the atria and ventricles. In this report, however, it will be used to indicate the presence of a consecutive series of A-V nodal impulses, whether these control the whole heart or only one set of chambers because of a conduction defect. No attempt is made to subdivide A-V nodal rhythm into upper, middle, and lower types. As was pointed out long ago,[3] regardless of the location of the A-V nodal pacemaker, the electrocardiogram records merely the temporal relationship between the onset of atrial and ventricular depolarization. For example, the atria are activated before the ventricles when retrograde is shorter than antegrade conduction time, although both times may be normal, short, or prolonged. Therefore, the temporal relationship between P and R in A-V nodal rhythm is not analogous to the P-R

TABLE 1. *A-V Conduction Defects*

- I. Primary heart block (anatomic defects of A-V junction or abnormal refractory period)
  - A. First degree (delayed conduction)
    - 1. antegrade
    - 2. retrograde
    - 3. bidirectional
  - B. Second degree (incomplete block)
    - 1. antegrade
    - 2. retrograde
    - 3. bidirectional
  - C. Almost complete block
    - 1. antegrade or retrograde, with complete block in opposite direction
    - 2. bidirectional
  - D. Complete (A-V dissociation)
    - 1. undirectional (with any of the above degrees of block in opposite direction)
    - 2. bidirectional
- II. Secondary A-V block, or interference (normal refractory period)
  - A. Ipsedirectional interference
    - 1. delayed conduction
    - 2. dropped beats
  - B. Contradirectional interference
    - 1. isolated
      - a. direct
      - b. delayed
    - 2. repetitive (interference dissociation, A-V dissociation due to interference)
      - a. undirectional with block in opposite direction, which may be:
        - 1. primary, complete or incomplete
        - 2. secondary, due to ipsedirectional interference
      - b. bidirectional
    - 3. interference dissociation with capture
      - a. atrial
      - b. ventricular
      - c. both atrial and ventricular
    - 4. combinations of primary or secondary heart block with interference dissociation
      - a. block above level of A-V nodal pacemaker
      - b. block below level of A-V nodal pacemaker

interval in a sino-atrial (S-A) rhythm, in which instance it measures the actual conduction time from one point in the heart to another. Similarly, a true R-P interval occurs only when an idioventricular impulse is conducted to the atria. In order to emphasize this distinction, in A-V nodal rhythm if a P wave precedes an R we shall refer to a P to R time rather than to a P-R interval, and likewise to an R to P time rather than an R-P interval when the P wave follows a ventricular complex.

A-V Conduction Defects

A working classification of disturbances in conduction through the A-V junction is presented in table 1.

A-V Block. The separation of A-V block into primary and secondary classes, as suggested by Zeisler,[4] has been found most useful. Primary block is due to an anatomic defect or abnormal refractivity of the A-V junction. The block may be of any degree from simple delayed conduction to complete A-V dissociation. Rarely block may be almost complete, with transmission of an impulse only during the supernormal phase of conduction.[5, 6] It is important to realize that block may affect only antegrade or only retrograde conduction, or both, or it may involve conduction in both directions to different degrees.

Secondary A-V Block. Secondary block is due to interference, in the presence of a normal refractory period of the A-V junction. There are 2 types of interference, as follows:

1. Ipsedirectional interference: This occurs when the heart beat is so rapid that one impulse falls closely upon the heels of a preceding one traveling in the same direction and finds the A-V junction refractory, with consequent delay or failure of conduction. Examples are paroxysmal atrial tachycardia with first degree A-V block, or atrial flutter with 2:1 A-V block.[2]

2. Contradirectional interference: In contrast, a second type of interference occurs when an impulse from the atrium finds the A-V junction refractory due to passage of a beat from a lower center back toward the atrium. The interference here is between 2 impulses moving in opposite directions and toward each other, that is contradirectionally. The interference may be direct, in which case the 2 waves of excitation meet head on and mutually obliterate each other. However, if one of the impulses precedes the other and is blocked, it may nevertheless set up a refractory period for subsequent passage of a contradirectional impulse. This phenomenon may be designated delayed contradirectional interference. An example is the prolonged P-R interval of the first beat following an interpolated ventricular extrasystole.[7] In this paper the term interfer-

ence implies the presence of the contradirectional type, unless otherwise specified.

Contradirectional interference may be isolated or repetitive; *repetitive contradirectional interference produces A-V dissociation.*

A-V Dissociation. In A-V dissociation the atria and ventricles beat independently of each other in response to their own pacemakers. A-V dissociation may be due to primary complete heart block or to contradirectional repetitive interference.

Interference Dissociation. This term is used in the strict sense of A-V dissociation *due to* interference. No attempt is made to distinguish complete from incomplete interference dissociation because, as pointed out by others,[8] with rare exceptions, a long tracing will prove that the dissociation is incomplete. Interference dissociation may be bidirectional or unidirectional with primary block in the opposite direction.

Capture. During interference dissociation capture is said to occur when favorable conditions of the refractory state permit an impulse from one center to pass through the A-V junction and control the entire heart for one or more beats. Ventricular capture, atrial capture or occasionally both may occur in any given case. The term capture is preferred to that of an interference beat because the latter usage may cause confusion with the concept of a blocked beat due to isolated interference.

Foci between which Interference Dissociation May Occur

Interference dissociation between a sinoatrial and an A-V nodal rhythm is the most common form. It may be regarded as the prototype of this arrhythmia, and its presence will be implied unless otherwise specified. However, interference dissociation can occur between 2 pacemakers in any part of the heart. It is even possible to have interference between 2 foci in a single heart chamber, without implicating the A-V junction. The theoretical foci between which interference dissociation may occur are assembled for reference in table 2. In all instances (in the absence of antegrade second degree A-V block) the lower focus forms impulses at a faster rate than the upper one. Obviously retrograde block must be present, protecting the slower upper focus. This block may be primary, of any degree, or secondary, due either to ipsedirectional or contradirectional interference. On the other hand, interference dissociation is possible in the presence of a faster upper than lower focus, if there is incomplete antegrade block, reducing the number of conductible beats. Paroxysmal tachycardia in an upper focus in the absence of A-V block may be dissociated due to interference from tachycardia in a lower center (fig. 17*e*). This combination of arrhythmias is termed simultaneous dissociated paroxysmal tachycardia.[14] Rarely there may be interference between several foci active at the same time.[2] Parasystole with simple interference[13] may be considered a variant of interference dissociation.

Table 2.—*Location of Foci Between Which Interference Dissociation Can Occur*

1. S-A Node	Lower portion of S-A node Atria A-V node His bundle Ventricles	
2. Atrium (Paroxysmal atrial tachycardia, flutter or fibrillation with block)[7, 9, 10]	Two atrial foci[8] A-V node His bundle Ventricles	Homogenetic or heterogenetic rhythms
3. A-V node (A-V nodal rhythm, tachycardia with block	Two A-V nodal foci[1] His bundle Ventricles	
4. Ventricles	Two ventricular foci	
5. Complete A-V block with dissociation between 2 foci above[11] or below the site of block		
6. Interference dissociation between more than 2 foci (for example, S-A rhythm with dissociation due to interference with ventricular extrasystoles and automatic beats)[9, 12]		
7. Ventricular parasystole with simple interference[13]		

Site of Interference

Interference between 2 contradirectional impulses may occur at any level between their starting points. The most common mechanisms are illustrated in figure 1. Thus, interference between an S-A and A-V nodal impulses may take place in the A-V node, in the atrium (atrial

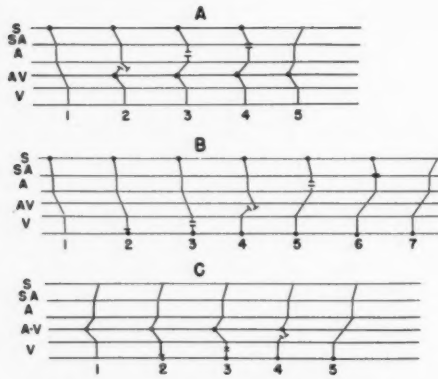

FIG. 1. Theoretical sites of interference between: (*A*) S-A and A-V nodal impulses, (*B*) S-A and idioventricular impulses, and (*C*) A-V nodal and idioventricular impulses. The customary conventions are employed to indicate the origin of impulses in the S-A node, A-V junction and ventricle, atrial and ventricular systoles, and S-A and A-V conduction.

fusion beat) or at the S-A junction. Interference between an S-A and a ventricular impulse may occur in proximity to the idioventricular focus, in the ventricle (ventricular fusion beat), in the A-V node, in the atrium (atrial fusion beat) or at the S-A junction. Finally, interference between an A-V nodal and an idioventricular rhythm may occur in the A-V junction, in the ventricle (ventricular fusion beat) or in the immediate vicinity of the idioventricular pacemaker. Rarely the site of interference may shift (figs. 8 and 16).

Zone of Potential Interference

A clear concept of isolated interference is essential to the understanding of the more intricate problems of interference dissociation. The mechanism of isolated interference can best be visualized with the aid of simplified diagrams.

In figure 2*a* let there be a pause in the sinus rhythm after P_2 so that an A-V nodal beat escapes. If retrograde is faster than forward conduction and an S-A beat does not appear before position P_4, the A-V nodal pacemaker will control the atria as well as the ventricles. However, if a normal sinus impulse arises at any time between P_3 and P_4, it will interfere with the A-V nodal escaped beat. The time

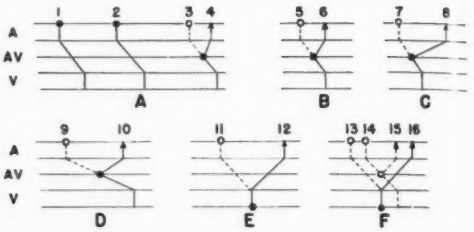

FIG. 2. Diagrammatic representation of the zone of potential interference. Solid dots and unbroken lines represent origin and conduction of active impulses. Open dots and broken lines represent theoretical position of interfering beats at the onset of the zone of potential interference.

interval between P_3 and P_4 may conveniently be termed "the zone of potential interference." (This zone is not to be confused with the phase of interference of Lewis and Master,[15] or the phase of concealed conduction of Langendorf and Pick,[7] which refers to that portion of the cardiac cycle between the absolute and relative refractory phase during which partial penetration of an impulse into the A-V junction takes place). In subsequent parts of figure 2 the pause preceding the A-V nodal or ventricular escaped beats is assumed to be constant, while conduction in either direction and the moment of appearance of oncoming S-A beats are the variables. In figure 2*b* forward and retrograde conduction times are equal and the zone of interference is slightly wider than in 2*a*. In figure 2*c* retrograde conduction is prolonged so that P_8 comes after the ventricular systole, and the zone of interference is correspondingly increased. In figure 2*d* forward conduction time is prolonged, and this mechanism also lengthens the zone of interference. Note that the zone of interference in A-V nodal beats is equal to the sum of forward and retrograde conduction times between the atrium and the site of the A-V nodal pacemaker.

From the foregoing considerations certain important deductions may be derived, as follows: 1. It may be anticipated that interference, and dissociation due to interference, are more likely to occur when the A-V nodal rhythm is of that type in which retrograde conduction time is prolonged, since the zone of potential interference is thereby increased. 2.

Since A-V nodal rhythm of this type is much less common than that with preceding atrial activation, the explanation for the infrequency of interference dissociation (as well as reciprocal rhythm) in clinical practice is apparent. 3. Prolongation of antegrade conduction time also lengthens the zone of potential interference, and therefore first degree A-V block is a predisposing factor for interference dissociation. 4. In A-V nodal escaped beats most commonly the temporal relationships are such that there is interference with an oncoming S-A impulse. 5. However, if an escaped beat controls the entire heart, statistically the type with preceding atrial activation should be most common, and in our experience this is true with respect to escaped beats after atrial or A-V nodal extrasystoles.

We have not observed an A-V nodal escaped beat with preceding atrial activation after ventricular extrasystoles. However, this phenomenon is theoretically possible, particularly if the ventricular impulse is conducted retrograde to the atrium and discharges the S-A node. In the latter event, the postextrasystolic pause and subsequent escape mechanism should be the same as following A-V nodal extrasystoles. Schott[16] presented 2 cases of ventricular extrasystoles with retrograde conduction, followed by A-V nodal escaped beats with P preceding R, which he considered unique. Schott explained the preceding atrial excitation in the escaped beats on the basis of facilitation.

In figure 2*e* the zone of interference of an idioventricular beat is shown. The duration of this zone is equal to the sum of forward and retrograde conduction times between the atria and the ventricles. In figure 2*f* the zone of interference (P_{13}–P_{16}) of an idioventricular beat is compared to one (P_{14}–P_{15}) of an average A-V nodal beat starting at the same time. The difference in duration of the 2 zones of interference is equal to the time required for conduction from the A-V nodal focus to the ventricle and back.

The following deductions regarding idioventricular beats seem logical: 1. Since the zone of interference of idioventricular beats exceeds that of atrionodal beats, retrograde conduction is statistically less likely following the former. 2. The zone of interference is of relatively greater importance late in atrial diastole. This fact has been confirmed incidentally by Kistin and Landowne,[17] and Bussan, Torin and Scherf,[18] who found that retrograde conduction occurs most often after those ventricular extrasystoles that come early in diastole. 3. The zone of interference is of particular significance when the heart rate is rapid because it will then occupy a greater proportion of diastole. 4. Moreover, if the zone of interference should exceed the duration of the atrial cycle length, retrograde conduction would be impossible at all times. These factors help explain the infrequency of ventricular capture and of retrograde conduction to the atria in paroxysmal ventricular tachycardia.

The diagrams in figure 2 have been simplified for our present purposes. Actually the problem is complicated by such factors as the zone of delayed contradirectional interference, the location of the A-V nodal pacemaker, unusual prolongation of the refractory period, variation in conduction through the A-V junction at different levels, facilitation, reentry and, finally, abnormalities in sino-atrial conduction.

Modes of Onset of Interference Dissociation

There are several ways in which interference dissociation may originate. These will be divided into 3 categories, as follows:

1. *Escape Mechanism*: (*Lower center slower than upper center*)

The A-V nodal focus may have a slower inherent rhythm than the S-A node, but it may fortuitously usurp control of the heart during a pause in the dominant rhythm. Such a pause may be due to deficient production of impulses (sinus arrest), blocked sinus impulses (sino-atrial block), and blocked impulses in the A-V node above the site of its pacemaker, or may follow extrasystoles and paroxysmal tachycardias of any type.[2] If the duration of the atrial pause exceeds the nodal cycle length, an A-V nodal escaped beat is to be expected. The escaped beat may control the entire heart, but more often it interferes with the oncoming sinus beat (fig. 2). The escape may be isolated,

but occasionally favorable temporal relationships permit a consecutive series of escaped beats, resulting in dissociation. Since the sinus rhythm is faster than the escape rhythm it must quickly regain control of the heart beat, and, therefore, interference dissociation of this type is necessarily short lived (fig. 19*a*).

2. *Homogenetic Rhythms: (Lower center slightly faster than upper center)*

Under certain conditions an A-V nodal focus may develop a slightly more rapid rhythm than the S-A node, and consequently control ventricular activation. If its rhythm is fast enough, the A-V nodal pacemaker will control the atria also. However, if the A-V nodal rhythm is only slightly faster than the S-A rhythm, interference dissociation may occur. The dissociation may be due to bidirectional interference or to forward interference and retrograde primary or secondary block. The onset of interference dissociation will be favored if the A-V nodal rhythm is of the type with preceding ventricular activation and consequently a wide zone of potential interference (fig. 2*c*). The A-V nodal rate may become faster than the S-A rate at any given moment under the following circumstances: 1. Depression of the S-A nodal rhythm, with the A-V nodal rate constant (figs. 4 and 5). 2. Slight acceleration of the A-V nodal rhythm with the S-A rate constant. 3. Combination of acceleration of the A-V and slowing of the S-A rhythms. 4 Depression of both pacemakers, with a greater effect on the S-A rhythm. 5. Acceleration of both rates but involving the A-V node to a greater degree.

In some cases it may be difficult to differentiate a homogenetic rhythm from a heterogenetic one, particularly when the rates of both foci are relatively rapid. This point is of more than academic importance because an active ectopic rhythm may require suppressive therapy, such as, quinidine, whereas no attempt should be made to abolish a potential escape rhythm.

3. *Heterogenetic Rhythms: (Lower focus much faster than upper one)*

Active rhythms may originate in lower centers which are much more rapid than the S-A rhythm and ordinarily should take command of the entire heart. However, if retrograde block is present, antegrade dissociation results. Therefore, paroxysmal A-V nodal and ventricular tachycardia with retrograde, but not forward block are examples of interference dissociation. Of course, the retrograde block may be of any type: primary, complete or incomplete, or secondary. In the last case, if the conductible retrograde rhythm is slightly faster than the S-A rhythm, interference may occur in the upper portion of the A-V node and thus there will be a combination of ipsedirectional and contradirectional retrograde interference. At very fast rates in paroxysmal A-V nodal or ventricular tachycardia with delayed retrograde conduction, the zone of potential interference might exceed the R-R interval and ventricular capture would therefore be impossible.

Duration of Interference Dissociation

Interference dissociation tends to be a transient arrhythmia and rarely persists for any appreciable time without interruption. In some patients it may be encountered at every examination over a period of months or years, but it is always interrupted at frequent intervals. Persistent interference dissociation is possible only in the following situations: 1. In the presence of retrograde block and a high degree antegrade A-V block, if the critical R to P interval for forward conduction, plus the P-R interval for conducted beats exceeds the automatic ventricular period.[19] 2. In paroxysmal ventricular tachycardia with retrograde block if the refractory period of the bundle plus the P-R interval exceeds the ventricular cycle length.[20] 3. In rare cases of synchronization of the 2 rhythms.[21–24]

Modes of Termination of Interference Dissociation

The termination of interference dissociation may take one of the following forms:

1. When dissociation is due to an accidental escape mechanism, as discussed previously it will of necessity be short-lived and the S-A pacemaker regains control of the heart after a few beats.

2. In homogenetic rhythms changes may

occur in the relative rates of the upper and lower pacemakers so that the sinus impulses obtain a clear lead and terminate the dissociation. These changes are the reverse of events favoring the onset of interference dissociation (fig. 13).

3. Interference dissociation may be abolished by various maneuvers or drugs affecting the ectopic focus to a greater degree than the S-A node. Thus normal sinus rhythm may be restored by forced breathing, carotid sinus pressure (fig. 15), exercise, change of posture, or the administration of atropine. (Paradoxically, in some cases interference dissociation may be precipitated by these same factors.)

4. If the A-V node should suddenly develop a sufficiently fast rhythm, simple A-V nodal rhythm may replace interference dissociation (figs. 8 and 9).

5. Interference dissociation may be abolished by a ventricular capture (or a reciprocal beat) which discharges the ectopic pacemaker (fig. 9).

6. As a result of ventricular capture, or other types of transition,[25,49] the sinus rhythm may be accelerated and take command of the heart (fig. 5).

7. An atrial capture may be followed by a run of A-V nodal rhythm when the retrograde beats discharge the S-A pacemaker, temporarily depressing its rhythmicity (fig. 9).

8. The transition from interference dissociation to normal sinus or A-V nodal rhythm may be abrupt or gradual. Indeed at times the one rhythm seems to slip imperceptibly into the other. This form of transition frequently is characterized by the presence of fusion beats (figs. 16 and 17*a*).[26]

9. At times the transition between the 2 rhythms may be accompanied by shifting of the pacemaker in the sinus node.[2]

10. Interference dissociation may be terminated by an atrial extrasystole which discharges the lower center on its way through the A-V junction (fig. 14). It is theoretically possible that a ventricular extrasystole with retrograde conduction could do the same thing.

Comparative Rates of the Two Rhythms

Classically in interference dissociation the lower rhythm is faster than the upper one. However, exceptions to the rule may be encountered, as follows:

1. Although the S-A rhythm is actually faster, the slower A-V nodal rhythm may escape after a pause, as previously described (fig. 19*a*).

2. Preceding the transition from interference dissociation to normal sinus rhythm there may be a short period during which the S-A nodal pacemaker warms up and is faster than the A-V nodal focus, but has not yet gained control of the heart beat (figs. 17 and 17*a*).

3. There may be varying degrees of S-A block so that the A-V rhythm is faster than the effective S-A rhythm.[27]

4. The sinus rhythm may be faster, but there may be A-V block above the site of the A-V nodal pacemaker.[9] If the internodal interval is shorter than the time between conductible S-A beats, interference dissociation results (figs. 10 and 11).

5. The A-V nodal rhythm actually may be faster than the sinus rhythm, with resulting interference dissociation. However, if there is co-existent second degree block below the level of the A-V nodal pacemaker, the antegrade conductible A-V nodal beats will be less frequent than the atrial beats.

6. If synchronization occurs, the 2 rhythms may run along at the same rate for varying lengths of time.

It is obvious, therefore, that an A-V nodal rhythm faster than the sinus rhythm is not a necessary criterion for the diagnosis of interference dissociation.

Aberrancy in A-V Nodal Rhythm

In A-V nodal rhythm most often ventricular conduction is slightly aberrant. At times the aberrancy may be very marked, with resulting bizarre QRS complexes. In the case of A-V nodal extrasystoles or paroxysmal tachycardia the aberrancy of the ventricular responses is due to the normal refractivity of the bundle branches, that is, ipsedirectional interference. This explanation obviously cannot apply to A-V nodal escape mechanisms. Prinzmetal and his group[28, 29] attributed the ventricular aberrancy in the Wolff-Parkinson-White syndrome as well as in A-V nodal escaped beats to accelerated conduction through special pathways within the A-V junction tissue. However, Pick and

Katz[30] have criticized this theory, and we concur with the opinion that it is untenable. Pick[31] suggested that the aberrancy of ventricular conduction from A-V nodal escaped beats is due to utilization of paraspecific pathways of conduction[32] by impulses originating in peripheral portions of the A-V node, in contrast to those originating more centrally. In order to confirm this theory it will be necessary to prove that the paraspecific fibers are actually functional.

Another possible explanation is that if the A-V nodal focus is located eccentrically its excitation wave may spread unevenly through the junction and reach one bundle branch in advance of the other. In this connection it has been shown that the A-V node is partitioned by longitudinal fibrous septa, which could account for the fact that longitudinal is more rapid than horizontal transmission[6, 27] We find this hypothesis particularly appealing, because it is compatible with Scherf's[33] theory of functional longitudinal dissociation in reciprocal rhythm, and also with the explanation for the occurrence of both atrial and ventricular captures in the same case (q.v.). The same theory may be invoked to explain changes in contour of retrograde P waves (fig. 9).

In rare instances it is possible for the A-V nodal beats to give rise to more normal looking QRS complexes than the sino-atrial beats. This phenomenon occurs in the Wolff-Parkinson-White syndrome with interference dissociation (fig. 19). The A-V nodal beats in the Wolff-Parkinson-White syndrome may show some ventricular aberrancy due to fusion with a portion of a sino-atrial impulse passing over the anomalous pathway.[26] In interference dissociation between an S-A and an idioventricular rhythm in the presence of bundle-branch block it is possible for the idioventricular beats to appear supraventricular in contour if they originate in the interventricular septum.[34]

In some cases it may be difficult, if not impossible, to differentiate A-V nodal escape with aberrant conduction from ventricular escape.

Relationship of the P Wave to QRS Complexes

In interference dissociation, due to the fact that the ventricular is faster than the atrial rate, the P wave appears to run up to the QRS complex, come abreast of it and finally pass it (figs. 8 and 9). This is the outstanding electrocardiographic manifestation of interference dissociation and is the main clue to its diagnosis. The progressive shortening of the P to R time has led to use of the term "reverse Wenckebach phenomenon."[35, 36] This term should be discarded because the P to R relationship in interference dissociation has nothing in common with second degree heart block. Moreover, the designation "reverse Wenckebach phenomenon" may cause confusion with the retrograde Wenckebach phenomenon in A-V nodal rhythm (fig. 9c).

When the P wave passes a QRS complex the following events may happen in subsequent beats. 1. Ventricular capture. 2. Atrial capture. 3. Synchronization or accrochage.[22]

Ventricular and Atrial Capture

Ventricular capture occurs when, without significant change in rate of either the upper or lower rhythms, the P wave passes the QRS, finds the bundle nonrefractory and is conducted to the ventricle (fig. 9). Other types of transition between the 2 rhythms involved in interference dissociation are not to be considered true captures.

With ventricular capture there may be normal atrioventricular and intraventricular conduction. However, frequently A-V conduction is delayed or the capturing beat may be blocked. If the blocked impulse discharges the atrionodal pacemaker, the effect of concealed conduction will be manifested by an irregularity in the ventricular rhythm.[37] The bundle branches may be in a relative refractory state so that the QRS complexes of the ventricular capture will be aberrant (an example of ipsedirectional interference). The ventricular capture in passing through the A-V node may discharge and depress its pacemaker, thus abolishing interference dissociation. If it does not discharge the A-V nodal pacemaker a

ventricular capture might be interpolated. Usually a ventricular capture has no effect on the S-A rhythm. However, in some cases the rate of the S-A pacemaker may be accelerated,[25, 49] and more rarely the S-A rate may slow down following a ventricular capture (fig. 7).

If conduction through the A-V junction is uniform the first ventricular cycle length following a capture may be the same, or nearly the same, as the usual nodal cycle length. If there is a localized delay in conduction of the ventricular capture below the site of the A-V nodal pacemaker (as compared to the usual A-V conduction) the next ventricular cycle will appear shortened.[37] On the other hand, if the capture depresses the A-V nodal pacemaker the next internodal interval may be prolonged and the effect may extend over several cycles. In interference dissociation with an idioventricular rhythm, an incomplete capture would cause a ventricular fusion beat.

Analogous events come into play with regard to atrial capture. If a retrograde atrial beat discharges and depresses the S-A nodal pacemaker, a run of uncomplicated A-V nodal rhythm may result. If the atrial capture is only partial, an atrial fusion beat appears. In an atrial capture interference may occur at the S-A junction (fig. 1-*A*4) so that the sinus rhythm will not be disturbed. In some cases an atrial capture may be accompanied by a reciprocal beat (fig. 9).

It is of interest that ventricular capture is much more frequent than atrial capture. Study of figures 2 and 3*a* will demonstrate that ventricular capture should be impossible unless there is retrograde block. Apparently in most cases this condition is met, and therefore atrial capture is encountered infrequently. In figure 3*a* the zone of interference of the blocked retrograde beat between P_1 and P_2 is evidently very short. Therefore P_4 falling at a distance beyond this zone, is conducted to the ventricle. P_2 comes during the refractory period of the bundle following the blocked retrograde beat and is not conducted (an example of delayed contradirectional interference).

Of exceptional interest are those cases in

FIG. 3. Possible mechanisms explaining occurrence of atrial and ventricular captures in the same case. *A*. Retrograde block. *B*. Simultaneous bidirectional conduction through A-V node.

which both atrial and ventricular captures occur. The simplest explanation for this phenomenon is that the retrograde block is intermittent. When retrograde block is absent an atrial capture would be expected; when present, ventricular capture would occur.

However, an alternate explanation may be offered. We have been impressed recently by observation of several cases in which there were both atrial and ventricular captures, accompanied by reciprocal rhythm (fig. 9).[1] Similar cases have appeared in the literature.[8, 38, 39] This suggests a relationship between bidirectional capture and reciprocal rhythm. If ventricular capture occurs in the absence of retrograde A-V block, the S-A impulse must somehow by-pass the A-V nodal impulse as shown in figure 3*b*. This could occur in the presence of functional longitudinal dissociation in the A-V node.[33] An A-V nodal beat may start out, be transmitted rapidly to the ventricle, and simultaneously spread toward the atrium at a retarded rate in a localized longitudinal pathway. Before the retrograde impulse can reach the atrium a sinus nodal impulse may have already activated the atrium and proceeded down the unexcited section of the A-V node, and finding the lower part of the A-V junction nonrefractory, be transmitted to the ventricle. Meanwhile the retrograde A-V nodal beat will be blocked at the atrial boundary owing to refractivity of the atria following the impulse P_5. In other words, simultaneous bidirectional conduction through the A-V junction could well account for the foregoing phenomenon. In the hypothetical instance in figure 3*b* if the beat P_5 had not occurred, there might have been a reciprocal beat as well as an atrial capture.

Heart Block and Interference

Interference dissociation is frequently associated with other forms of heart block.

Antegrade Block. First degree A-V block produces a prolonged zone of potential interference and consequently increases the chances of interference (fig. 2*b*). Persistent dissociation due to interference may result when the ventricular cycle length is shorter than the combined lengths of the refractory period of the bundle and the P-R interval.[20]

The presence of second degree A-V block above the level of the A-V nodal pacemaker makes interference dissociation possible in cases in which the S-A rhythm is faster than the lower one. This is the underlying mechanism of paroxysmal atrial tachycardia, flutter, and fibrillation with interference dissociation. Whenever the automatic ventricular cycle is longer than 1 sinus period but shorter than 2 atrial cycles, dissociation with interference in the presence of 2:1 A-V block should be considered.[19] There is a critical period for the R to P time which determines when a S-A impulse will be conducted. Usually the R to P time exceeds the normal sinus period but this is not always true (fig. 10). If the critical R to P interval plus the time required for forward conduction exceeds the ventricular period, persistent dissociation may occur and closely resemble A-V dissociation due to complete primary block.[19]

Rarely in interference dissociation incomplete A-V block occurs below the site of the A-V nodal pacemaker. When a capturing beat is blocked below the A-V nodal pacemaker, the condition has been termed double interference[40] or dissociation with ladder type of interference.[41]

In the presence of complete A-V block interference dissociation is possible between 2 foci above, or 2 foci below the site of block.

Retrograde Block. Since in interference dissociation the A-V nodal pacemaker is usually the faster one, it would control the entire heart unless there were retrograde block. It is to be emphasized that this block may be of several types.

1. Probably in most cases retrograde conduction is slower than forward conduction. This factor as well as first degree retrograde block lengthens the zone of potential interference (fig. 2*c*), and thereby predisposes to interference dissociation, particularly at rapid rates.

2. Complete primary retrograde block may be present. In this event no impulses from the A-V node would enter the atrium under any circumstances.

3. When the ventricular rate is excessively rapid, as in paroxysmal A-V nodal or ventricular tachycardia, incomplete primary or secondary block may occur. The rate of the retrograde conductible beats may be slightly faster than the rate of the S-A beats and therefore retrograde interference dissociation will occur.

Differential Diagnosis

There are a number of arrhythmias that must be differentiated from interference dissociation. The most important are the following:

1. First degree heart block with a long P-R interval, with the P wave lying close to the preceding QRS. Tracings of this type closely resemble interference dissociation with synchronization. However, in a long tracing when the heart rate changes either spontaneously or in response to the sinus reactions the P-R interval will remain constant.

2. Second degree A-V block with a P-R interval longer than the P-P interval.[2] This is seen as a manifestation of 2:1 block, or in the Wenckebach phenomenon. In the former instance the relationship will become clear when the rate of the sinus rhythm changes. The Wenckebach phenomenon is differentiated because of the marked irregularity in the ventricular rhythm.

3. Almost complete block with V-A or A-V response. Differentiation of this condition from interference dissociation has been briefly discussed in the report of case 7. Winternitz and Langendorf[11] suggested that complete, or almost complete, antegrade block and normal retrograde conduction may lead to interference dissociation in reverse. However, in such cases it is necessary to rule out the presence of al-

most complete retrograde block, with conduction only during the supernormal phase.

4. Complete A-V block. As has been pointed out the rate of the atrial as compared to the ventricular rhythm is not an absolute criterion for differentiation, since the ventricular rate may be faster than the conductible atrial rate in interference dissociation, and rarely in complete block the atrial rate may be slower than the ventricular rate. The main point of differentiation is that in complete block in long tracings there will never be any evidence of conduction across the A-V junction.[9]

5. Atrial fibrillation with complete block presents the same picture as atrial fibrillation with interference dissociation. However, when the dissociation is of short duration, it is probably due to interference.

6. Interference dissociation between an S-A and A-V nodal rhythm with aberrant ventricular conduction may sometimes be confused with interference dissociation between S-A and idioventricular rhythms. The latter in turn would have to be differentiated from interference between an S-A and A-V nodal rhythm in the presence of bundle-branch block. Long tracings recording the onset and termination of interference dissociation, or the presence of isolated extrasystoles or escaped beats should resolve this problem. Ventricular captures or fusion beats are diagnostic of an idioventricular rhythm.[42]

7. Ventricular parasystole requires special consideration in the differential diagnosis of interference dissociation. In parasystole the rhythm of the lower center is slower than the upper one. This is probably the most important distinction. The ventricular center is protected from the higher center by an entrance block, that is, there is unidirectional forward block into the parasystolic center and retrograde interference. This is the reverse of ordinary interference, in which there is forward interference and retrograde block. The differentiation from the mechanism shown in figure 1-*B*2 where a ventricular focus is not discharged by a sinus beat is that in the latter instance the focus is protected by interference and not by a permanent block, and potentially the ventricular focus could be discharged at other times in the cardiac cycle; in parasystole the ventricular focus is protected at all times. In interference dissociation the 2 foci may be protected from one another by block or interference at a distance; for example, the sinus nodal pacemaker may be protected from a ventricular impulse during ventricular tachycardia by retrograde block in the A-V junction. In parasystole the protecting block is in the immediate vicinity of the ventricular pacemaker. In rare instances ventricular parasystole may complicate interference dissociation between 2 other foci.[13]

Presentation of Cases

Case 1

E. B. This 63-year-old white man had recently developed the anginal syndrome. By coincidence he suffered a sudden attack of coronary thrombosis while a routine electrocardiogram was being made. The accompanying lead I (fig. 4) was obtained within a few minutes of the onset of pain, before any medication had been given.

The atria are under the control of the sinus nodal pacemaker. Phasic sinus arrhythmia is present, with an atrial cycle length varying from 0.84 to 1.04 seconds. On the other hand, the internodal interval is fixed at 1.01 seconds. The P waves numbered 4, 5, 6, 9, and 10 are conducted to the ventricle, terminating cycles 0.86 to 1.01 seconds in duration. Interference dissociation occurs in the remaining portions of this tracing. The ventricular complexes in response to sinus nodal impulses differ slightly in contour from those of A-V nodal origin. Respiratory variations in the form of QRS also occur throughout the tracing. At the transition from normal sinus rhythm to interference dissociation, between R_6 and R_7, the cycle length is equal to the usual internodal interval for this case. This suggests that the A-V nodal focus is located low down in the junctional tissues, since the A-V nodal impulse must have begun to develop immediately preceding the onset of QRS_6.

Comment. This case illustrates one of the simplest forms of interference dissociation, with sinus arrhythmia and a fixed internodal interval. As the S-A rate waxes and wanes, there is a shift between normal sinus rhythm and interference dissociation. The ventricular complexes in response to A-V nodal stimuli are slightly aberrant.

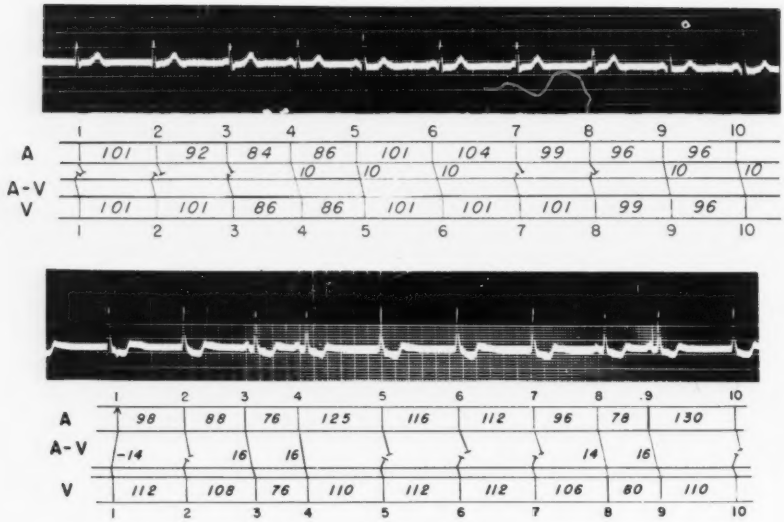

FIG. 4 *Top.* Case 1. Lead I.
FIG. 5 *Bottom.* Case 2. Lead II.

Case 2

W. R. This patient was a 58-year-old Negro man with hypertensive heart disease and digitalis intoxication. A short strip of lead II is shown in figure 5. The first beat is of A-V nodal origin with retrograde slower than antegrade conduction time. The R to P time is 0.14 second. P_2-R_2 represents isolated interference between S-A and A-V nodal impulses. The third and fourth beats are of normal sinus origin, with a P-R interval of 0.16 second and an R-R interval of 0.76 second. The sinus rhythm is depressed after P_4 allowing the A-V node to escape and a bidirectional interference dissociation results. After P_7 the sinus rhythm accelerates and regains command of the heart at P_8. At the transition from interference dissociation to normal sinus rhythm the atrial cycle length shortens and P_9 also is conducted to the ventricle. Following P_9, S-A rhythmicity is depressed and interference occurs.

The inherent rhythm of the A-V node is regular, with a cycle length of 1.12 seconds. The intervals, R_4–R_5 and R_9–R_{10}, introducing the first nodal beats following sinus beats, are slightly shorter, measuring 1.10 seconds. This slight discrepancy in timing indicates that the A-V nodal impulses must have started to form shortly before the onset of QRS_4 and QRS_9. The ventricular complexes of A-V nodal origin are slightly aberrant. Between P_4 and P_7 the A-V nodal rhythm is actually faster than the S-A rhythm, yet the A-V nodal pacemaker does not gain control of the atria, despite the absence of retrograde block. However, owing to the fact that retrograde is longer than forward conduction, the zone of potential interference is increased, and dissociation occurs. Of course, if the S-A node did not quicken its pace and take command of the heart at P_8, the A-V nodal impulses eventually would have effected an atrial capture.

Comment. The interesting features in this case are as follows: 1. Interference dissociation occurs during periods of depression of the S-A nodal pacemaker. 2. The interference dissociation is bidirectional. 3. Retrograde conduction time from the A-V node to the atrium is longer than forward conduction time to the ventricle. 4. The resulting time differential, with widening of the zone of potential interference, favors establishment of interference dissociation rather than atrionodal rhythm. 5. The transition from interference dissociation to normal sinus rhythm is accompanied by enhancement of the S-A nodal rhythmicity. (Blumgart and Gargill[25] ascribed this phenomenon to improvement in coronary artery blood flow to the S-A node following 2 ventricular systoles in rapid succession. Cutts[49] suggested that coronary blood flow to the sinus node may be maximal when the atria and ventricle beat in their normal sequence.)

Case 3

I. I. This patient was a 62-year-old Negro woman with hypertensive and arteriosclerotic heart dis-

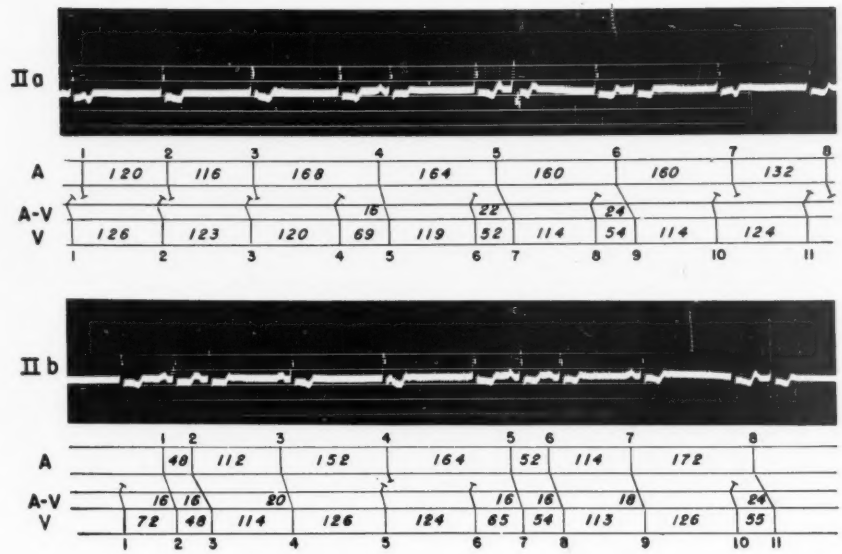

FIG. 6. Case 3. Selected strips of lead II.

ease, and digitalis intoxication. Selected strips of lead II are shown in figure 6. In strip *a*, for the first 3 cycles interference dissociation is present between S-A and A-V nodal pacemakers. The atrial cycle length increases abruptly from 1.16 seconds between P_2 and P_3 to 1.68 seconds between P_3 and P_4. At the same time the ventricular cycle length decreases from 1.26 between R_1 and R_2, to 1.23 between R_2 and R_3, and 1.20 seconds between R_3 and R_4. The combination of the lengthening of the P-P interval and the shortening of the R-R interval causes P_4 to fall outside of the refractory period of R_4 and, therefore, to be conducted to the ventricle. There is no evidence of atrial activity accompanying R_4, although sufficient time is available for retrograde conduction. In long tracings in this case a retrograde atrial beat was never recorded and, therefore, evidently complete retrograde block is present. The interval R_4–R_5 measures 0.69 second and the ventricular beat R_5 appears normal in contour. Following R_5, 2 pairs of ventricular systoles occur. They consist of an A-V nodal beat followed by a normal sinus beat (pseudoreciprocal rhythm).[39] Since the S-A impulse encounters the relative refractory phase of the bundle, both atrioventricular and intraventricular conduction are impaired. The P-R interval between P_5 and R_7 is 0.22 second and the interval R_6–R_7 measures 0.52 second. The interval R_8–R_9 is 0.54 second and the P-R interval between P_6 and R_9 is 0.24 second. The interval R_8–R_9 is slightly longer than R_6–R_7 and there is a lesser degree of aberrancy of R_9 as compared to R_7. Interference dissociation recurs in the last 2 cycles of this strip.

In strip *b*, the first beat is of A-V nodal origin with retrograde block. P_1 falls outside of the refractory phase of R_1, and is conducted normally after a P-R interval of 0.16 and an R-R interval of 0.72 second. P_2 is an atrial extrasystole, followed by a normal ventricular response after a normal P-R interval and an R-R interval of 0.48 second. The same sequence, A-V nodal beat, normal sinus beat and atrial extrasystole, occurs between R_6 and R_8. The interval between the normal sinus beat P_7 and the atrial extrasystole P_8 is 0.54 second and intraventricular conduction is normal. R_{10} is an A-V nodal escaped beat and R_{11}, a normal sinus beat with an aberrant ventricular response after a prolonged P-R interval of 0.24 and an R-R interval of 0.55 second. The cycle preceding an atrial extrasystole is shorter than most of the intervals between escaped beats and normal sinus beats, yet intraventricular conduction is normal after atrial extrasystoles and aberrant in the latter instance. The explanation for this may be that the atrial extrasystoles occur after a comparatively short cycle (R_1–R_2 and R_6–R_7 in strip *b*), while the sinus beats following escaped beats terminate a short cycle after a long one (R_5–R_6 and R_7–R_8 in strip *a*, and R_9–R_{10} in strip *b*). Since the refractory period of the junctional tissues varies directly with the length of the preceding cycle, the cause for this phenomenon is apparent.[43] It is of interest that the P-P interval shortens following an atrial extrasystole, and the beats P_3 and P_7 are conducted. These short intervals may be due to improved blood supply to the S-A node following 3 beats in close succession, that is, R_1, R_2, R_3 and R_6, R_7, R_8 in strip *b*.[25]

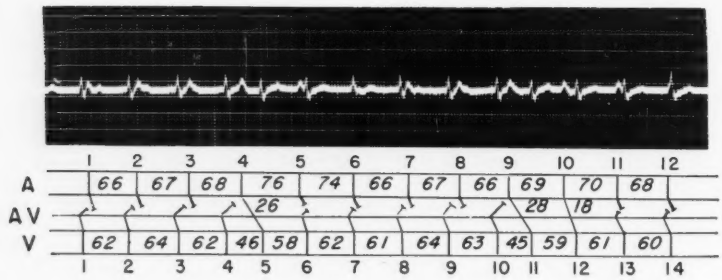

FIG. 7. Case 4. Lead II.

Comment. The salient features demonstrated in this tracing are as follows: 1. Interference dissociation in the presence of marked sino-auricular depression. 2. Pseudoreciprocal rhythm. 3. Aberrant intraventricular conduction in relation to the length of the preceding cycles. 4. Effect of atrial extrasystoles on the subsequent sinus rhythm. 5. Termination of interference dissociation by a combination of acceleration of the ventricular rhythm and depression of the sinus rhythm. (This is an apparent paradox, since the same factors in the presence of a normal sinus rhythm may produce interference dissociation.)

Case 4

A. W. Figure 7, a selected strip of lead II, was obtained from a 60-year-old white man with arteriosclerotic heart disease. No medication that might have influenced the rhythm had been given.

Interference dissociation between an S-A and A-V nodal rhythm is present. The rates of both the S-A and A-V nodal foci vary independently. In the first 4 cycles the P-P interval lengthens progressively while the A-V nodal rate is fairly constant. As a result, P_4 comes far enough beyond R_4 to fall in the relative refractory phase of the bundle, and it is conducted to the ventricle after a P-R interval of 0.26 and an R-R interval of 0.46 second. The ventricular capture following P_9 occurs after a P-R interval of 0.28 second and an R-R interval of 0.45 second. Following the capture by P_4 the atrial cycle length increases to 0.76 second. There is a less marked increase in the P-P interval of 0.69 second after the capture of P_9. The latter temporal relationship is such that it allows a second sinus beat to be conducted (P_{10}–R_{12}). The lengthening of the interatrial cycle length embracing the ventricular capture is unusual. An increase in vagal tone caused by the early captured ventricular beat may be sufficient to overcome any effect of increased blood flow and hence cause slowing of the S-A rate. An alternate and perhaps preferable explanation is that the intervals P_4–P_5 and P_9–P_{10} would have increased, even if there were no intervening ventricular beat, due to the presence of sinus arrhythmia, which of itself set up conditions favorable for the capture. The impulse from the S-A node which gives rise to the ventricular capture passes through the A-V nodal focus and discharges it. The foreshortening of the internodal intervals between R_5–R_6 and R_9–R_{10} is due to the fact that there is a delay in the passage of the capturing impulse below the site of the A-V nodal focus.

Comment. This tracing demonstrates interference dissociation between S-A and A-V nodal rhythms in which the 2 vary in rate independently and according to no set pattern. Ventricular capture occurs on 2 occasions, with foreshortening of the succeeding internodal cycle length, due to a conduction delay below the level of the A-V nodal pacemaker.[27] Following ventricular capture the atrial cycle length increases, but this is probably a fortuitous event due to the presence of sinus arrhythmia.

Case 5

D. A. This 60-year-old white man had had a thyroidectomy because of a toxic nodular goiter. He was receiving digitalis, and postoperatively was given quinidine for persistent atrial fibrillation. The tracing in figure 8 was obtained after termination of the atrial fibrillation. Selected strips, cut from a long lead II, are presented for analysis.

In strip *a* the atrial mechanism cannot be definitely determined. The ventricular rhythm is perfectly regular. The ventricular complexes are of the RS type and are followed by small positive deflections that at first glance might be thought to be R prime waves or upright P waves.

In strip *b* right carotid sinus pressure was applied between the arrow markers. The ventricular rhythm slows gradually and the eighth ventricular beat interferes with a preceding normal S-A beat.

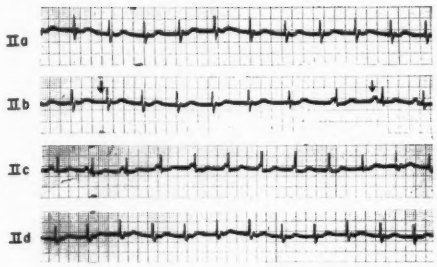

FIG. 8. Case 5. Selected strips of lead II.

The next 3 beats are of normal sinus origin. At this point it might be suggested that the positive deflection after the S wave in strip *a* is an upright P wave with interference dissociation and synchronization between the S-A and A-V nodal rhythms. However, strips *c* and *d* clearly delineate the rhythm.

Following the first beat in strip *c* interference dissociation occurs, with the P wave running up to the QRS complex, coming abreast of it at R_8 and passing it at R_9. At R_{11} the A-V node takes control of the entire heart. The P wave coinciding with R_{10} is probably an atrial fusion beat. (Compare fig. 1*A*, mechanisms 1, 2, 3, and 5.)

The A-V nodal rhythm continues throughout strip *d*. Towards the end of the tracing the relationship of P to QRS is similar to that in strip *a*. The retrograde P wave in this case is of the minus-plus type with a prominent late upright deflection. It is the final portion of the retrograde P wave that appears after the QRS complexes in strip *a* and resembles an upright P wave. Also, superimposition of the negative phase of the P wave upon the S wave causes the latter to appear deeper.

Comment. This case demonstrates an A-V nodal rhythm that could be converted at will to interference dissociation and then normal sinus rhythm by carotid sinus stimulation. Stimulation of the carotid sinus caused slowing of both the S-A and A-V nodal rhythms but affected the latter to a greater degree. As recovery from carotid stimulation took place the rates of both rhythms increased but the A-V nodal rhythm became relatively more rapid than the sinus rhythm, so that first interference dissociation and then simple A-V nodal rhythm resulted.

Case 6

M. P. This 60-year-old white man was suffering from arteriosclerotic and pulmonary heart disease. Selected strips of a long lead II obtained on July 1, 1954, are shown in figure 9. The patient was not receiving digitalis or quinidine at that time.

In strip *a* the first P wave is conducted to the ventricle after a P-R interval of 0.14 second. Following this interference dissociation occurs between S-A and A-V nodal rhythms. The atrial cycle length for the most part is 0.53 to 0.54 second in duration. Possibly due to changes in vagal tone, the atrial cycle length increases to 0.58 second between P_3–P_4 and P_{11}–P_{12}. The A-V nodal cycle length measures 0.47 to 0.49 second. Following the normal beat at the beginning of this strip the P wave runs up to the QRS complex, comes abreast of it at R_4, and begins to pass it at R_5. P_7 occurs long enough after R_8 to fall within the relative refractory phase of the bundle and it is conducted to the ventricle after a P-R interval of 0.24 second. This ventricular capture shortens the R-R interval to 0.44 second. Two conducted sinus beats, P_8 and P_9, follow the ventricular capture. This phenomenon may be due to the fact that the S-A impulses P_7, P_8, and P_9 in passing through the A-V node discharged and temporarily depressed its pacemaker.[44] However, it soon picks up enough speed to interfere again with the sinus rhythm at P_{10}. Interference dissociation continues to the end of the strip. The interval R_9–R_{10} is shortened due to the fact that the P-R interval preceding R_9 is prolonged while the next P-R interval is normal.[27]

At the beginning of strip *b* interference dissociation is present. The third atrial impulse is conducted and a ventricular capture results. As in strip *a*, 2 normal sinus beats follow the capture. Interference recurs between P_6 and R_7 and continues to P_9, which is an atrial capture. Since the A-V nodal rhythm is faster than the S-A rhythm at this point, a run of A-V nodal beats ensues (P_9, P_{10}, and P_{11}). Conduction of the retrograde beat P_{11} is prolonged to 0.22 second. This retrograde beat re-enters a pathway in the A-V node long enough after R_{12} to be conducted to the ventricle with a manifest forward conduction time of 0.25 second. The re-entrant beat apparently discharges and depresses the A-V nodal pacemaker, causing a pause in the atrial rhythm of 0.58 second, which is terminated by a normal sinus beat, P_{12}. Interference dissociation then recurs. It is possible that a blocked re-entrant beat occurred after P_{10}, setting the stage for the reciprocal beat at P_{11}. The same factor of concealed conduction of a previous beat causing areas of refractivity in the bundle might account for the aberrancy of P_{11} as compared to other retrograde P waves in this tracing. It is of interest that in this short tracing are seen normal sinus rhythm, interference dissociation, ventricular capture, atrial capture, A-V nodal rhythm, and reciprocal rhythm. Similar cases have been reported by others.[8, 38, 39]

Strip *c* begins with a run of A-V nodal rhythm with a progressively increasing R to P time, which suddenly lengthens to 0.24 second after R_4 (the

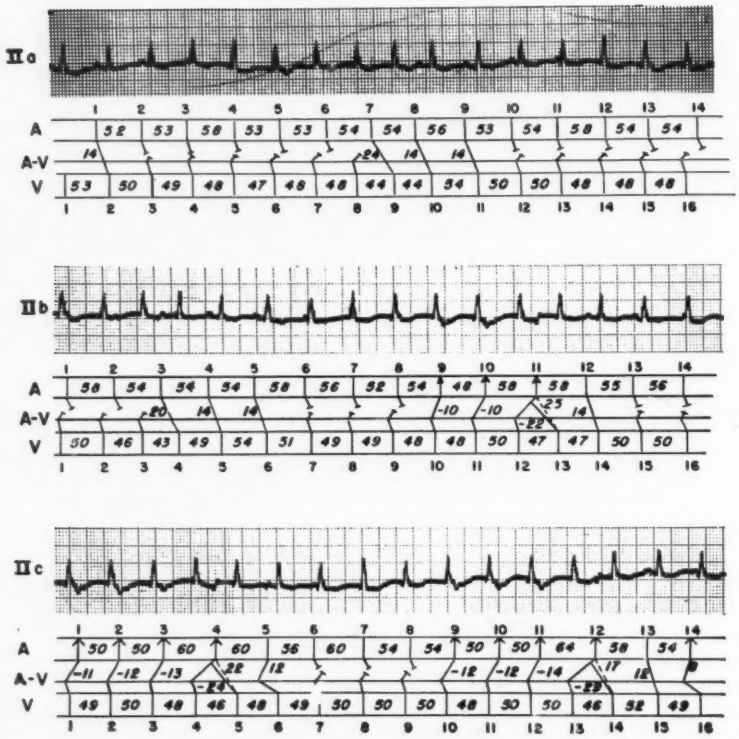

FIG. 9. Case 6. Selected strips of lead II.

retrograde Wenckebach phenomenon). This results in an increase in the atrial interval, P_3–P_4, without a change in the corresponding R-R interval. Therefore, the lengthening of the atrial cycle is due simply to an increase in retrograde conduction time and not to a change in rate. P_4 falls far enough after R_4 to accommodate a re-entrant mechanism and R_5 is a reciprocal beat. Again note the aberrancy of P_4. P_5 may be an atrial fusion beat. The fact that the retrograde beat P_5 precedes R_6 may reflect a prolongation of antegrade relative to retrograde conduction time due to the proximity of R_6 to R_5. Following P_5 dissociation recurs and persists until R_{10}, when the A-V nodal pacemaker assumes command of the whole heart. Reciprocation occurs following P_{12}. The reciprocal beat discharges the A-V nodal pacemaker and a normal sinus mechanism ensues at P_{13}. The last beat in this tracing is either an A-V nodal beat or an interference beat. In the first reciprocal beat the R to P time is 0.24 second and the P to R time is 0.22 second, while in the second reciprocal beat R to P measures 0.29 and P to R, 0.17. In the reciprocal beat in strip *b*, R to P measures 0.22 and P to R, 0.25 second. This conforms with the well-known phenomenon that in reciprocal rhythm there is an inverse relationship between R to P and P to R times.[45]

Comment. The following interesting features are illustrated by this case: 1. The close relationship of normal sinus rhythm, interference dissociation, atrial capture, ventricular capture, and reciprocal rhythm. 2. Demonstration of all these variants in a single short tracing. 3. The depressing effect on either the S-A or A-V nodal rhythms by premature discharge of one focus by an impulse from the other. 4. The possibility of concealed conduction of a blocked re-entrant beat setting the stage for reciprocal rhythm in the following beat, and explaining variations in the contour of the atrial complexes. 5. The apparent shortening of the ventricular cycle length following a ventricular capture with a prolonged P-R interval.

Case 7

G. G. The clinical diagnosis of this 56-year-old white man was arteriosclerotic heart disease, en-

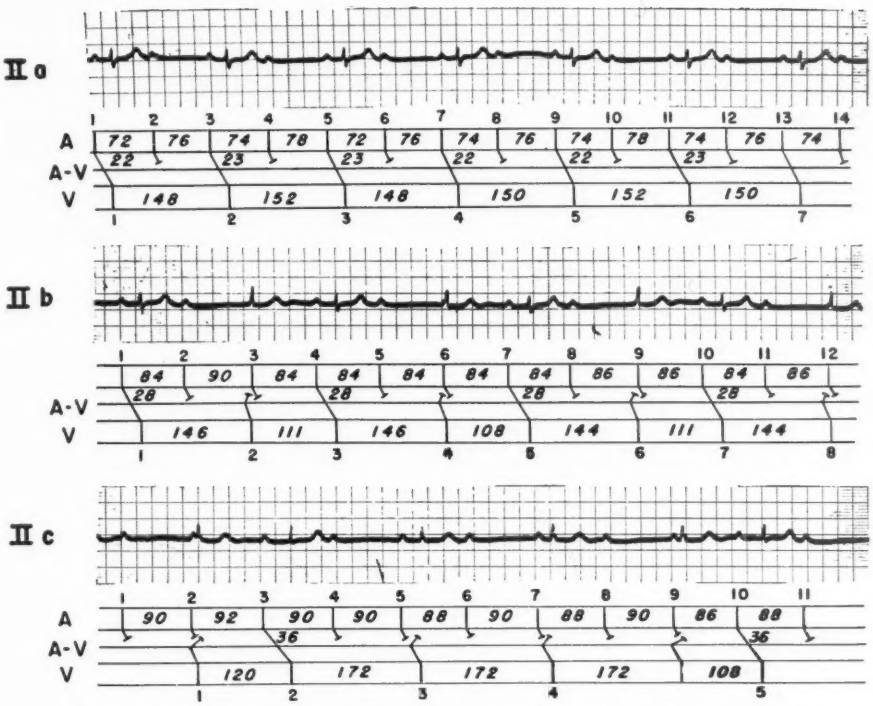

FIG. 10. Case 7. Selected strips of tracings (lead II) obtained on 3 different occasions.

larged heart, second degree A-V block, nodal escaped beats, interference dissociation, and the anginal syndrome. In childhood he had had diphtheria, which may have been an etiologic factor for the heart block.[46] Selected strips of lead II obtained on different occasions are presented in figure 10.

In strip *a*, normal sinus rhythm with 2:1 A-V block is present. The atrial cycle length varies from 0.72 to 0.78 second, due to ventriculophasic sinus arrhythmia.[47] The P-R interval of conducted impulses measures 0.22 to 0.23 second. The ventricular cycle length is between 1.48 and 1.52 seconds.

In strip *b* every third atrial impulse only is conducted to the ventricle, after an interval of 0.28 second. Each conducted beat is followed by a blocked P wave, and the latter in turn by interference between an S-A impulse and an A-V nodal escaped beat. The atrial rate is slower than in strip *a*: the cycle length measures 0.84 to 0.90 second. The escaped beats occur after a pause of 1.44 to 1.46 seconds, thus causing a bigeminal rhythm.[12] The form of the escaped beats is slightly aberrant, as indicated by absence of the S wave which identifies the sinus beats. The fact that the dominant S-A rhythm is slower in strip *b* than in strip *a* allows time for escape of the lower focus.

In strip *c* interference dissociation is present. The S-A rhythm is slower than on the 2 previous occasions, with a cycle length of 0.86 to 0.92 second. The internodal interval (1.72 seconds) also is longer than in strip *b*. Ventricular captures occur at R_2 and R_5, after a P-R interval of 0.36 second. It may be assumed that basically 2:1 A-V block is present, since this conduction defect was constant during the previous year. The ventricular rate is faster than that of the conductible atrial beats, and since there is retrograde block interference dissociation results. The QRS complexes of A-V nodal origin have the same contour as the escaped beats in strip *b*.

In strip *b* isolated escape occurs, while in strip *c* interference dissociation is encountered, although in both instances the ventricular is faster than the conductible atrial rate. However the ventricular rate is relatively more rapid in strip *b*, (average P-P interval 0.85 second, internodal interval 1.45 seconds) than in strip *c* (P-P interval 0.89 second, R-R interval 1.72 seconds). As a result, in strip *b* the escaped beats fall early enough before the next P wave to allow the latter to be conducted to the ventricle, whereas in strip *c* the P wave following the nodal beats most frequently arrives during the refractory period of the bundle. This allows repetitive interference before a ventricular capture finally occurs.

The rhythm in strip *c* might easily be mistaken for almost complete heart block with occasional

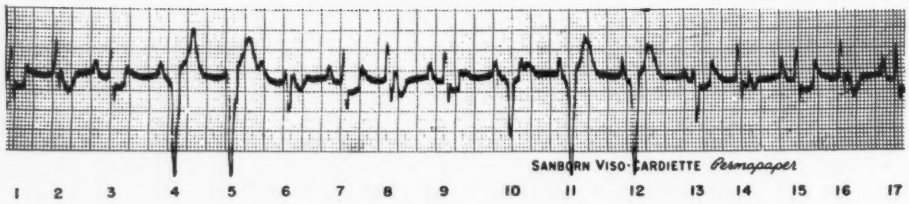

FIG. 11. Case 8. Lead II.

A-V response. To prove the existence of the latter arrhythmia it is necessary to demonstrate a critical interval during which A-V conduction occurs, so that any P wave falling before or after this interval will be blocked.[5] Upon analysis of the long tracing from which strip *c* was obtained these criteria were not fulfilled. Conduction did not take place unless the R to P time was greater than 0.70 second. However, an upper limit of R to P time after which block would again result could not be demonstrated. Another point against the possibility of almost complete block in this case is that over a long period of observation complete block did not develop.

Comment. This case demonstrates interference dissociation in the presence of second degree A-V block. It fulfills the criteria set down for this arrhythmia by Dressler, Roesler, and Specter.[19] The genesis of the arrhythmia from 2:1 A-V block to second degree A-V block with nodal escape and finally to interference dissociation, and the relation of these rhythms to the atrial and ventricular rates are demonstrated.

Case 8

E. W. This 68-year-old white man was being treated for congestive heart failure due to hypertensive and arteriosclerotic heart disease. He also had progressive muscular dystrophy, with possible cardiac involvement. Following administration of a mercurial diuretic he had an unusually marked response that precipitated digitalis intoxication, evidenced by paroxysmal atrial tachycardia with block. Figure 11 illustrates the arrhythmia. Paroxysmal atrial tachycardia is present with shifting of the ectopic pacemaker. There are obvious differences in contour of the P waves preceding the fourth, thirteenth, and fifteenth ventricular beats. The P-P interval averages 0.34 second. The minor variations in atrial rhythm may be related to shifting of the ectopic pacemaker or to ventriculophasic arrhythmia secondary to the dropped beats.[47] Second degree A-V block is present with the Wenckebach phenomenon. For the most part each third atrial beat is blocked. In the pause following QRS_3 there is a pair of ventricular escaped beats. QRS_6 is either a ventricular escaped beat or fusion beat. A similar sequence occurs after QRS_9. The tenth, eleventh, and twelfth QRS complexes are ventricular in origin. QRS_{13} is probably a ventricular fusion beat. The interval between idioventricular beats measures 0.60 to 0.66 second. The R-R interval of the conducted beats varies from 0.46 to 0.62 second.

Comment. In this case the actual atrial rhythm is faster than the idioventricular rhythm. However, due to the presence of second degree antegrade A-V block, the idioventricular rhythm is faster at times than the conductible atrial rhythm. Thus, interference dissociation occurs between a paroxysmal atrial tachycardia and an idioventricular rhythm.

Case 9

P. K. This 67-year-old white man was admitted to the hospital on June 17, 1954, following an attack of acute coronary thrombosis. An electrocardiogram just prior to admission showed complete heart block. Later that day second degree A-V block was present, with nodal escaped beats and interference dissociation. Interference dissociation was recorded at all subsequent examinations until July 12, 1954. Selected strips (lead II) of several electrocardiograms taken during this period are presented for analysis.

In figure 12 the first 3 beats are of normal sinus origin with P-P intervals of 0.68 to 0.72 second. The first P-R interval is prolonged to 0.24 second, the next 2 intervals to 0.26 second. P_4 is blocked and R_4 is in response to an A-V nodal escape, which touches off a run of interference dissociation. Although during the rest of this strip the S-A pacemaker is slightly faster than the atrionodal one, it cannot quite gain control of the ventricles and interference dissociation persists. R_{10} might be in response to P_{11}, but the corresponding P-R interval is probably too short for this patient. Interest centers about the pause in the ventricular rhythm between R_3 and R_4, which is 1.16 seconds in duration. If P_4 were conducted through the site of the A-V nodal pacemaker, and discharged it, there should have been a longer pause before R_4 because the in-

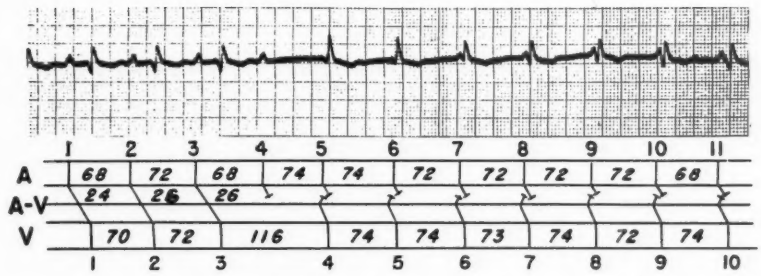

FIG. 12. Case 9. Lead II.

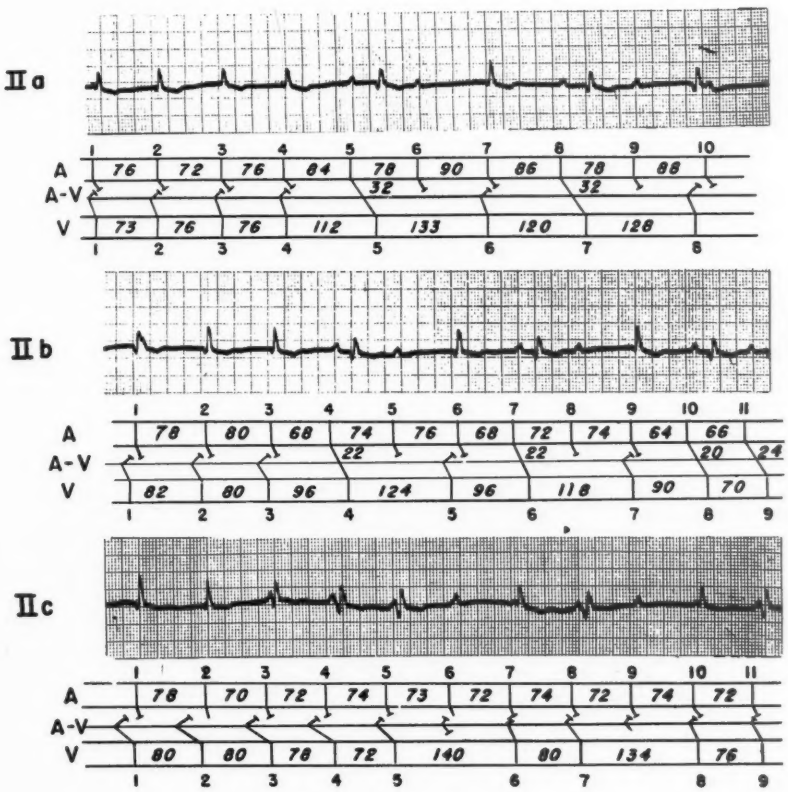

FIG. 13. Case 9. Selected strips of lead II.

terval P_4 to R_4 is too short with respect to the subsequent internodal cycle length to accommodate this mechanism. Therefore P_4 must be blocked above the level of the A-V nodal pacemaker. Probably the most acceptable explanation for the pause is that the A-V nodal pacemaker is depressed by the sinus rhythm between P_1 and P_3, and when P_4 is blocked a delay occurs before the A-V node can initiate its own rhythm.

In figure 13, strip *a*, interference dissociation is present between the first 4 S-A and A-V nodal beats. The rates of the 2 pacemakers are quite similar. Following the fourth atrial and ventricular impulses both pacemakers slow down but the A-V node is depressed to a greater degree, allowing P_5 to be conducted to the ventricle after a prolonged P-R interval of 0.32 second. P_6 falls within the absolute refractory period of the bundle after R_6

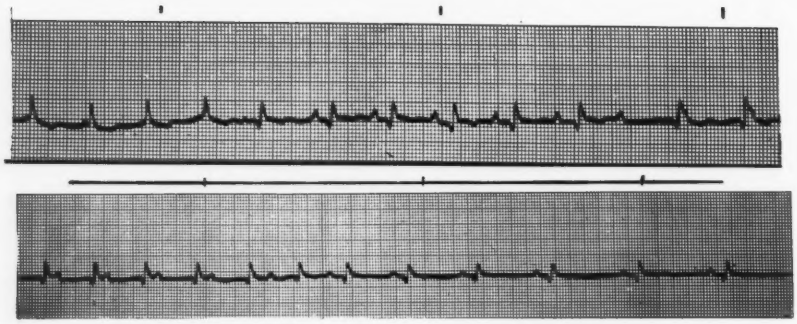

FIG. 14 *Top*. Case 9. Lead II.

FIG. 15 *Bottom*. Case 9. Lead II. Carotid sinus stimulation signaled by horizontal line above tracing.

and is blocked above the level of the A-V nodal pacemaker. There is delay in formation of the next nodal beat, with the interval measuring 1.33 seconds between R_5 and R_6. P_7 encounters interference, P_8 is conducted and P_9 is blocked. Interference recurs between R_8 and P_{10}.

In strip *b*, for the first 3 cycles interference dissociation is present. However, following P_3 the atrial rhythm suddenly speeds up while the A-V nodal rhythm slows down, and P_4 is conducted after a P-R interval of 0.22 second. P_5 and P_8 are blocked and followed by nodal escaped beats with interference. The inherent nodal rhythm must be slower in the second half of this strip to allow P_7 and P_{10} to be conducted without interference.

In the 2 preceding strips and in figure 12, the block was presumed to be above the level of the A-V nodal focus with a pause before initiation of an A-V nodal beat. In strip *c*, a different mechanism for the pause following blocked P waves is encountered. Interference dissociation is present throughout this tracing. Between R_1 and R_5 the ventricular rhythm accelerates and the cycle length decreases from 0.80 to 0.72 second. There is a pause of 1.40 seconds between R_5 and R_6 during which P_6 is blocked. This sequence differs from those in strips *a* and *b*, and figure 12, in which the P waves preceding the blocked beats are conducted. In strip 2*c* the blocked beat P_6 is not preceded by a conducted one. Furthermore, P_6 occurs long enough after R_5 to have been conducted to the ventricle. The key to solution of this problem is furnished by analysis of the spacing of the ventricular beats. The ventricular rate speeds up before the pause after R_5, the shortest interval precedes the pause and the first cycle following the pause is greater (0.80 second) than that preceding it (0.72 second), and the pause itself is shorter than the sum of any 2 consecutive short cycles. This arrangement is typical of the Wenckebach phenomenon and suggests the presence of an area of block below the level of the A-V nodal pacemaker.[2, 7] The nodal beat between R_5 and R_6 is concealed, with antegrade block, while interfering in a retrograde direction with the oncoming sinus beat, P_6. Similarly, concealed interference could account for the blocked beat P_9.

Figure 14 shows the effect of an atrial extrasystole during interference dissociation. The fifth P wave represents an extrasystole that is conducted to the ventricle. En route it discharges and depresses the A-V nodal pacemaker, with subsequent restoration of normal sinus rhythm. The P-R interval increases slightly in subsequent beats and the eleventh P wave is blocked above the level of the A-V nodal pacemaker. Interference dissociation then recurs.

Figure 15 demonstrates one effect of carotid sinus pressure in interference dissociation. Left carotid sinus pressure causes the S-A rhythm to slow down to a greater degree than the A-V nodal rhythm. This causes the P waves to fall further beyond QRS and allows a ventricular capture by the fifth atrial beat. Normal sinus rhythm is established at a slow rate but the A-V nodal pacemaker continues in a depressed state, so that the S-A rhythm persists to the end of this tracing.

Comment. The following are some of the interesting features in this case: 1. Interference dissociation in the presence of an atrial rhythm faster than the A-V nodal rhythm. 2. Onset of atrial nodal rhythm with a pre-automatic pause. 3. Slowing down of both S-A and A-V nodal rates, but the latter to a greater degree, allowing the S-A node to take control of the heart. 4. S-A nodal rhythm speeding up while A-V nodal rhythm slows down, breaking up interference dissociation. 5. Presence of block below the level of the A-V nodal pacemaker with the Wenckebach phenomenon, and concealed interference. 6. Termination of interference dissociation by a conducted atrial

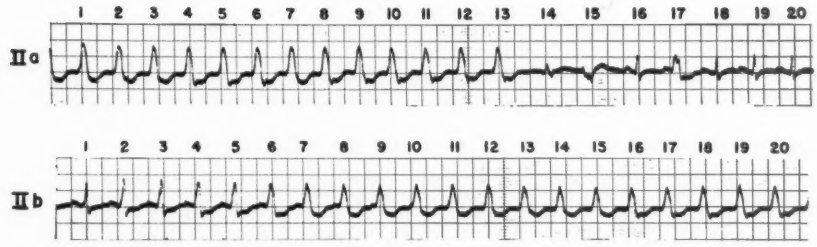

FIG. 16. Case 10. Selected strips of lead II.

extrasystole which discharges and depresses the A-V nodal pacemaker. 7. Effect of carotid pressure on interference dissociation, causing restoration of normal sinus rhythm by slowing the S-A more than the A-V nodal rate.

Case 10

A. V., a 62-year-old white man, was suffering from arteriosclerotic heart disease with congestive failure and multiple disturbances of rhythm. At the time the tracing in figure 16 was obtained he was receiving digitalis. Ventricular tachycardia is present at the beginning of strip *a* and for the first few beats the atrial mechanism is not visible. Immediately following R_4 a retrograde P wave can be detected. After 3 retrograde atrial beats a P wave drops out. Following R_8, retrograde conduction is resumed until termination of the ventricular tachycardia after R_{13}. Then there are 2 ventricular escaped beats of multifocal origin. The first normal sinus beat occurs at R_{16} and introduces a sinus tachycardia. R_{17} is a ventricular extrasystole. The P-P interval during the sinus tachycardia measures 0.48 second, as compared to an R-R interval of 0.46 second during the ventricular tachycardia.

In strip *b* the tracing starts with a sinus tachycardia. This is followed by dissociation due to interference with a ventricular tachycardia that is only slightly faster than the sinus rhythm. At first the interference occurs in the ventricle with production of ventricular fusion beats (R_2 through R_6). At R_6 the site of interference shifts to the A-V junction, and after R_{16} retrograde conduction to the atria occurs and the ventricular focus controls the entire heart. (Compare with fig. 1*B*, mechanisms 1, 3, 4 and 7.)

Comment. In this case a sinus tachycardia competes for control of the heart with a slightly faster ventricular tachycardia. Because of slight difference in rates, the transition from one rhythm to the other is gradual and marked by the presence of ventricular fusion beats. The dissociation is due to bidirectional interference, since there is normal retrograde as well as antegrade conduction. Malinow and Langendorf[26] present a strikingly similar case in their authoritative paper on the mechanism of fusion beats.

Case 11

T. M. This 60-year-old white man was suffering from arteriosclerotic heart disease complicated by multiple arrhythmias. Long leads were obtained on frequent occasions, and selected portions of lead II are presented for analysis.

In figure 17, strip *a*, normal sinus rhythm is present at an approximate rate of 75 per minute. The first 2 QRS complexes are of supraventricular origin. The P-R interval measures 0.24 second. The fifth to the tenth ventricular systoles constitute a run of idioventricular rhythm with interference dissociation. The idioventricular cycle length is 0.76–0.84 second. Thus, for part of the time during dissociation the ventricular rhythm is faster than the atrial rhythm, but preceding the transition to normal sinus rhythm it is actually slower for a short time. As might be anticipated when the 2 independent rhythms have about the same rate, fusion beats appear at the onset and termination of interference dissociation (R_3, R_4, and R_{11}). The onset of interference dissociation coincides with a slight increase in rate of the idioventricular pacemaker and a slight decrease in the S-A rate, and the reverse occurs in the transition from idioventricular to normal sinus rhythm.

In strip *b*, the first 2 beats are of normal sinus origin. The third ventricular complex is an extrasystole from the same focus (designated focus 1) as the idioventricular rhythm in strip *a*. The fifth ventricular complex is an extrasystole from a second idioventricular focus, designated focus 2. It is followed by another extrasystole from focus 1 and then by 2 automatic beats of similar origin. Thus, interference dissociation is present from the fifth to the eighth ventricular beats.

In strip *c* the second beat is a ventricular extrasystole from focus 2. A pair of similar extrasystoles occur at R_4 and R_5, followed by a run of automatic

beats from the same focus. The idioventricular rhythm originating in focus 2 is interrupted by an interpolated ventricular extrasystole from focus 1 (QRS_7). The eleventh beat is a ventricular capture. QRS_{12} is of normal sinus origin. The last 2 beats are a ventricular extrasystole and an automatic beat from focus 2.

In strip *d* paroxysmal A-V nodal tachycardia is present and is terminated by carotid sinus pressure, signaled by the solid black line. Preceding the end of the tachycardia there are 2 ventricular extrasystoles that do not disturb the A-V nodal rhythm. In strip *e*, A-V nodal tachycardia is present, with a cycle length of 0.42 second. The first, third, and fifth ventricular beats are extrasystoles and the last one introduces a short run of ventricular tachycardia. A second run of paroxysmal ventricular tachycardia is present from the seventeenth to the twenty-first ventricular systoles. In this tracing, during ventricular tachycardia retrograde conduction from the ventricle to the atrium does not occur owing to interference below the level of the A-V nodal pacemaker. On other occasions in this case, during sustained ventricular tachycardia, retrograde conduction to the atrium did occur.

Comment. This case shows the following nteresting features: 1. Interference dissociation between a normal sinus rhythm and multifocal idioventricular rhythms. 2. Idioventricular rhythm preceded and followed by fusion in the ventricle between supraventricular and idioventricular beats. 3. Idioventricular rhythm triggered off by ventricular extrasystoles. 4. Idioventricular rhythm with interference dissociation interrupted by interpolated ventricular extrasystoles. 5. Simultaneous dissociated atrionodal and ventricular tachycardia.

Case 12

T. S. This 64-year-old white man was suffering from multiple myeloma. Frequent electrocardiograms showed the presence of the Wolff-Parkinson-White syndrome. Short strips of the standard limb leads and precordial leads V_1 and V_4 are shown in figure 18 for purposes of orientation. The P-R interval measures 0.12 second and the QRS interval also is 0.12 second. A typical Wolff-Parkinson-White pattern is present, with positive delta waves in leads V_1 and V_4, and a small negative delta wave in lead II.

On July 7, 1955, unusual disturbances in rhythm

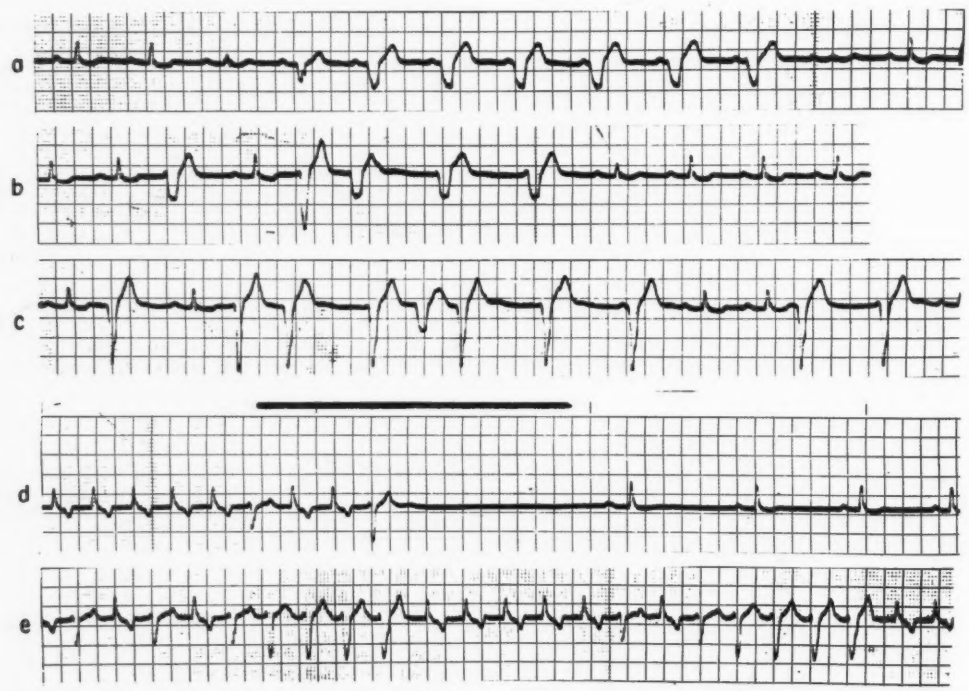

FIG. 17. Case 11. Selected strips of lead II obtained on different occasions.

developed, and 2 selected strips of lead II are presented for analysis in figure 19. In strip *a*, the dominant atrial rhythm is of normal sinus origin interrupted by atrial extrasystoles after each normal beat. P waves numbered 4, 5, and 7 are not clearly visible due to superimposition upon QRS complexes. Their position has been approximated after comparison with similar intervals in this tracing. For example, the time between P_3 and P_6 is the same as between P_{11} and P_{14}; and the interval P_6–P_8 is analogous to P_8–P_{10}. The coupling of the extrasystoles to the sinus beats is fixed at 0.52 second, with the exception of the first one, in which the pre-extrasystolic cycle measures 0.46 and the returning cycle 0.72 second. The returning cycle throughout the rest of the tracing is usually 0.68 second. The sum of the intervals preceding and following extrasystoles is 1.20 seconds for the most part, corresponding to the interval between 2 normal sino-atrial cycles in strip *b*. The QRS complexes in response to the atrial extrasystoles differ slightly in contour from those of S-A origin. This aberrancy is due to differences in the extent of pre-excitation of the ventricle, depending upon the distance of the ectopic focus from the anomalous atrioventricular connection. The QRS complexes that follow normal P waves at positions 9, 11, 13, and 15 differ from one another, from the usual Wolff-Parkinson-White complexes for this case, and also from those QRS complexes of A-V nodal origin. They probably represent fusion between a nodal escaped beat and an impulse from the atria traversing the anomalous A-V pathway.[26] The post-extrasystolic interval, 0.68 second, approaches that of the internodal cycle between R_4 and R_7 (0.66 second). The P-R interval of the S-A beats and the atrial extrasystoles is between 0.10 and 0.12 second.

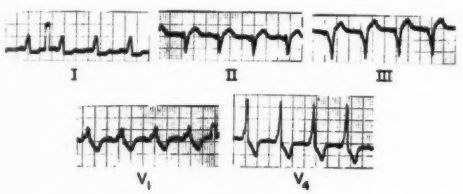

FIG. 18. Case 12. Standard limb leads and precordial leads V_1 and V_4.

The pause following the first atrial extrasystole P_2, is longer than the others in this tracing; and it is terminated by a nodal escaped beat that introduces a run of interference dissociation. The internodal cycle length is 0.66 second. This interval is longer than the average R-R interval during the remainder of this tracing, although it is shorter than most of the post-extrasystolic intervals, which measure 0.68 second. The fortuitous timing, however, allows a short run of dissociation. The QRS complexes in response to the A-V nodal focus measure 0.08 second and are almost entirely upright, with a small terminal S wave. The S-T segments are depressed and the T waves inverted. The atrial extrasystole P_8 occurs early enough in the cycle to capture the ventricle, discharge the A-V nodal focus and thus terminate the dissociation. It is of interest that in this tracing one atrial extrasystole induces interference dissociation, while another abolishes it. The nodal rhythm is interrupted by a premature ventricular contraction at R_4.[48]

In strip *b*, P_1 is probably an extrasystole, followed by a pause of 0.72 second, which allows the A-V

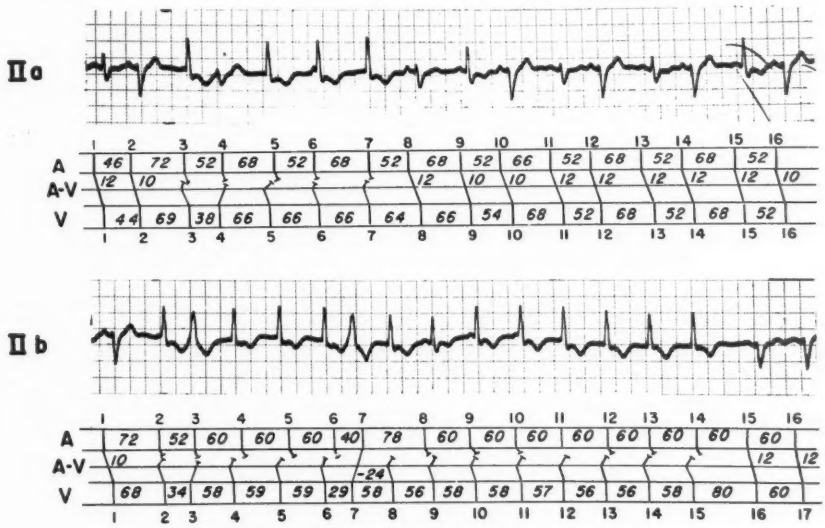

FIG. 19. Case 12. Selected strips of lead II.

node to escape. Following P_2 the atrial rhythm is regular, with a cycle length of 0.60 second except for the interval P_6–P_7. The ventricular cycle length in response to the A-V nodal pacemaker varies from 0.56 to 0.59 second and is shorter than the P-P interval. P waves cannot be clearly seen at positions 3, 11, 12, 13, and 14. In the thirteenth, fourteenth, and fifteenth ventricular complexes the S wave disappears and the S-T segment approaches the isoelectric line, probably due to superimposition of P waves upon the late portion of ventricular depolarization. QRS_9 is probably a fusion beat, similar to QRS_9 and QRS_{15} in strip *a*.

R_3 and R_7 are ventricular extrasystoles. R_7 is followed by a retrograde atrial impulse that discharges the S-A node and causes the succeeding P-P interval to lengthen to 0.78 second. R_3 is apparently from the same focus as R_7, but it is not followed by retrograde conduction and the atrial rhythm is not disturbed. Apparently an atrial extrasystole is superimposed on R_3, thus giving rise to interference in the A-V junction between an atrial and ventricular extrasystole. The internodal interval increases spontaneously after R_{15} and allows resumption of normal sinus rhythm with Wolff-Parkinson-White type responses.

Comment. This case demonstrates the following interesting features: 1. The Wolff-Parkinson-White syndrome with return to normal ventricular excitation in the presence of A-V nodal rhythm. 2. Varying types of ventricular fusion in the presence of the Wolff-Parkinson-White syndrome, following S-A nodal beats, atrial extrasystoles, and A-V nodal escaped beats. 3. Interference dissociation initiated and terminated by atrial extrasystoles. 4. Termination of interference dissociation by spontaneous depression of an A-V nodal pacemaker. 5. Interference between atrial and ventricular extrasystoles. 6. Ventricular extrasystoles with retrograde conduction to the atrium in the presence of A-V nodal rhythm with interference dissociation, an unusual type of atrial capture.

A similar case has been presented by Malinow and Langendorf.[26]

Summary

Contradirectional interference results when 2 stimuli arising in different foci in any part of the heart spread in opposite directions toward each other. Interference dissociation is defined as that type of dissociation which is due to repetitive contradirectional interference.

The electrocardiograms of 12 cases have been selected for analysis to illustrate many of the important features of interference dissociation.

The various centers between which dissociation may theoretically occur are listed for reference. This series includes examples of dissociation due to interference between the following pairs of rhythms: Normal sinus rhythm and A-V nodal rhythm, normal sinus rhythm and multifocal idioventricular rhythms, sinus tachycardia and paroxysmal ventricular tachycardia, paroxysmal atrial tachycardia with block and idioventricular rhythm, simultaneous dissociated paroxysmal A-V nodal and ventricular tachycardias, and normal sinus rhythm and A-V nodal rhythm in the presence of the Wolff-Parkinson-White syndrome.

Interference may occur at any level between the points of origin of the 2 rhythms, and the most common sites of interference are illustrated diagrammatically.

Interference at the upper end of the A-V junction is of particular importance, and a clear understanding of isolated interference in this region is of help in resolving some of the more difficult problems of dissociation. For this reason the concept of the zone of potential interference is introduced. This is the time interval in the cardiac cycle during which interference between an A-V nodal, or ventricular, and oncoming S-A beat may be anticipated. Certain important deductions are derived from theoretical considerations of the zone of potential interference.

The various mechanisms leading to the onset and termination of interference dissociation are described, and the rates of the dissociated rhythms are compared.

Aberrancy of the ventricular response to A-V nodal impulses is discussed. This phenomenon is ascribed to uneven spread of the excitation wave from an eccentrically located focus, due to the fact that in the A-V node longitudinal is faster than horizontal transmission.

Ventricular and atrial captures are considered in detail. Of particular interest is the occasional occurrence of both types of capture

in the same case. This paradox is explained on the basis of either intermittent retrograde block or simultaneous bidirectional conduction through the A-V node in the presence of functional longitudinal dissociation. The relationship of other forms of heart block to interference dissociation is pointed out. Heart block predisposes to, and frequently complicates, interference dissociation.

A differential diagnosis between interference dissociation and other disturbances of rhythm is presented.

Interference dissociation is one of the most complex arrhythmias and familiarity with all its possible variations is essential to the correct interpretation of any given tracing.

Summario in Interlingua

Interferentia contradirectional resulta quando 2 stimulos a origine in differente focos in alicun parte del corde se propaga in direction contrari le un verso le altere. Dissociation per interferentia es definite como le typo de dissociation que es causate per repetitive interferentia contradirectional.

Le electrocardiogrammas de 12 casos esseva seligite e analysate como illustration de multes del importante aspectos de dissociation per interferentia.

Le varie centros inter le quales dissociation es theoricamente possibile es listate pro objectivos de referentia. Iste serie include exemplos de dissociation causate per interferentia inter le sequente pares de rhythmos: Normal rhythmo sinusal e rhythmo nodal atrio-ventricular; normal rhythmo sinusal e multifocal rhythmos idioventricular, tachycardia sinusal e tachycardia ventricular paroxysmal, tachycardia atrial paroxysmal con bloco e rhythmo idioventricular, tachycardias nodal atrio-ventricular e ventricular dissociate simultanee, e normal rhythmo sinusal e rhythmo nodal atrio-ventricular in le presentia del syndrome Wolff-Parkinson-White.

Interferentia pote occurrer a non importa qual nivello inter le punctos de origine del 2 rhythmos. Le plus commun sitos de interferentia es illustrate diagrammaticamente.

Interferentia al extremitate superior del junction atrio-ventricular es de importantia particular. Un comprension precise de interferentia isolate in iste region es de adjuta in resolver certes del plus difficile problemas de dissociation. Pro iste ration le concepto del zona de interferentia potential es introducite. Illo es le intervallo de tempore in le cyclo cardiac durante le qual interferentia pote esser expectate inter un pulso nodal atrio-ventricular o ventricular e un pulso sino-atrial in preparation. Certe deductiones importante es derivate ab considerationes theoric del zona de interferentia potential.

Le varie mechanismos que effectua le declaration e le termination del dissociation per interferentia es describite, e le rapiditate del dissociate rhythmos es comparate.

Aberrantia del responsa ventricular a impulsos nodal atrio-ventricular es discutite. Iste phenomeno es ascribite a un propagation inequal del unda excitatori ab un foco de location excentric, in consequentia del facto que in le nodo atrio-ventricular le transmission longitudinal es plus rapide que le transmission horizontal.

Capturas ventricular e atrial es considerate in detalio. Le occurrentia occasional de ambe typos de captura in le mesme case es de interesse particular. Iste paradoxo se explica super le base de intermittente bloco retrograde o de simultanee conduction bidirectional a transverso le nodo atrio-ventricular in le presentia de un functional dissociation longitudinal. Es signalate le relation inter altere formas de bloco cardiac e dissociation per interferentia. Bloco cardiac es un factor que predispone a dissociation per interferentia e que frequentemente complica lo.

Es presentate un diagnose differential de dissociation per interferentia e altere disturbationes de rhythmo.

Dissociation per interferentia es un del plus complexe arrhythmias. Familiaritate con omne su variationes possibile es essential in le interpretation correcte de omne registration particular.

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Edwards, J. E.: Correlations in Coronary Arterial Disease. Bull. New York Ac. Med. **33:** 199 (March), 1957.

The material in this report came from patients dying in the hospital or at home under the care of physicians associated with the clinic or from autopsies done at the request of the coroner's office. Studies included cutting cross sections of epicardial vessels at regular intervals of 3 to 5 mm. and making transverse slices of the ventricles with microscopic examination of muscle from portions of the ventricles supplied by all branches of the coronary arteries. Significant coronary lesions were found in these patients, the highest incidence being in the age range from 50 to 59 years, where 75 per cent of the individuals had lesions. A correlation is made with the clinical circumstances of coronary artery disease. The author points out that in those patients with coronary artery disease and acute myocardial infarctions clinically, the mechanism of death is difficult to establish. Of 133 patients studied, 57 or 43 per cent died with evidence of myocardial failure. Thirty-one or 23 per cent of the patients died with repeated attacks of chest pain and without evidence of myocardial failure. This was diagnosed as coronary failure and there was no pathologic evidence of new infarction. Twenty or 15 per cent of the patients died of rupture of the heart. The rupture of the heart resulted first from a dissection in the endocardium with bleeding into the myocardium, and a final dissection of the hematoma through the epicardium into the pericardial space. In the 133 patients, only 8 who died had associated thromboembolic complications. In 250 patients with coronary artery disease in whom acute infarction had occurred in the past, 64 or 26 per cent died suddenly without evidence of repeated myocardial infarction. The author stresses that patients with coronary artery disease, including patients with healed myocardial infarction may die on the presumed basis of acute myocardial ischemia without infarction.

HARVEY

ABSTRACTS

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METABOLIC EFFECTS ON CIRCULATION

Bartter, F. C., Liddle, G. W., Duncan, L. E., Jr., Barber, J. K., and Delea, C.: The Regulation of Aldosterone Secretion in Man: The Role of Fluid Volume. J. Clin. Invest. **35:** 1306 (Nov.), 1956.

The factors governing the production of aldosterone have not yet been defined. Careful metabolic studies described in this paper suggest that the extracellular fluid volume rather than sodium per se mediates the regulation of aldosterone secretion. Thus, aldosterone secretion was decreased when the extracellular fluid volume was increased. This held true whether or not the *intra*cellular water was increased, decreased, or left unchanged. On the other hand, an increased aldosterone secretion was produced when extracellular fluid volume was decreased. This held true whether or not the intracellular water was decreased or left unchanged. Both circulating and total body potassium could be excluded as mediators of the volume control of aldosterone secretion. The authors suggest that the normal control of sodium and water homeostasis depends on a dual "feed-back" mechanism in which aldosterone produces an increase in serum sodium concentration, which results in a rise of extracellular fluid volume. The increase in volume then serves to inhibit further aldosterone secretion. There was no evidence relating to the mechanism by which the volume change effects are transmitted to the adrenal cortex. The authors point out that it had been shown previously that nephrosis, cirrhosis with ascites, and cardiac failure are characterized by aldosterone secretion in excess of normal in spite of increases in extracellular fluid volume.

WAIFE

Ginsburg, M., and Brown, L. M.: Effect of Anesthetics and Hemorrhage on the Release of Neurohypophysial Antidiuretic Hormone. Brit. J. Pharmacol. **11:** 236 (Sept.), 1956.

In anesthetized rats, the antidiuretic activity in external jugular blood was about 0.1 mU. vasopressin/ml. before, and about 7 mU./ml. after hemorrhage. It seems reasonable to conclude that during hemorrhage, neurohypophysial antidiuretic hormone is liberated into the circulation in increased amounts. Two distinct and separate phases in this liberation could be discerned. The first phase was associated with the initial fall in blood pressure, whereas the second phase was delayed and usually took place when the blood pressure had been less than 50 mm. Hg for about 15 min. It is tempting to suggest that the immediate release is due to nervous mechanisms, whereas the delayed release is mediated by the liberation of ferritin and adenosine triphosphate from the anoxic liver and muscle.

AVIADO

PATHOLOGY

Gallo, P. A.: A Study on the Topographical and Quantitative Relations between Capillaries and Fibres of the Conduction System of the Heart and on Their Functional Significance. Cardiologia **29:** 241, (No. 4) 1956.

Histologic studies are reported concerning the blood supply of the A-V conduction system in sheep and cattle. The author found that in contrast to ordinary myocardium specific nodal muscle fibers are separated from the capillaries by a considerable space filled with connective tissue. This, he feels, causes a delay in oxygen supply to the fibers, leads to slowing of metabolic processes in the specific musculature, and retardation of impulse transmis-

sion through the A-V node, and may thus be the explanation of the normal P-R interval. The investigations were extended specifically to the artery of Haas, a branch of the posterior coronary artery that runs along the base of the interatrial septum to the A-V node and the bundle of His. Due to this particular anatomic situation this artery seems to be unaffected by the forceful contraction of the ventricular septum and blood supply to the A-V conduction system is maintained during both systole and diastole. This, however, cannot significantly enhance the blood supply to the A-V node considering the scarcity of capillaries in this area as well as their separation from the specific muscle fibers.

PICK

Tuci, P., and Cinti, G.: The Pathogenesis of the Metastenotic Dilatation of the Pulmonary Artery in Different Experimental Conditions and in the Light of the Histochemical Changes of the Wall. Arch. De. Vecchi Anat. Pat. **24:** 645 (June), 1956.

In 1 group of 10 rabbits a circular stenosis of the pulmonary artery at its root was produced by ligature. In a second group an eccentric stenosis was obtained, without involving the whole circumference of the vessel. In a third group the adventitia was cauterized by loosely tying around the vessel a thread soaked in hydrochloric acid "40 per cent." The animals were killed at intervals varying between 63 and 105 days. It was found that the animals of the first group showed stenosis and poststenotic dilatation: those of the second group showed only stenosis; and the third group showed only a dilatation. The animals of the first 2 groups had cardiac hypertrophy. The microscopic examination of the areas of dilatation showed changes of the elastic fibers and histochemical changes similar to those observed in the poststenotic dilatation in man. It was concluded that the hemodynamic factors were not essential to the production of the poststenotic dilatation: in these experiments the altered trophism of the vascular wall produced by damage of the vasa vasorum was the anatomic basis of the dilatation.

CALABRESI

Könn, G.: The Pathological Morphology of the Pulmonary Vessels in A Study of the Etiology and Sequelae of Chronic Pulmonary Hypertension. Chronic Cor Pulmonale. Beitr. path. Anat. **116:** 273 (No. 2), 1956.

The pathologic changes of the pulmonary arteries in 52 patients with chronic cor pulmonale may be divided in 2 classes: (a) changes independent of the pulmonary hypertension; in a temporal sense these changes are "prehypertensive" and are considered causative of the hypertension; (b) secondary "posthypertensive" changes, considered to be an effect of pulmonary artery hypertension. Prehypertensive changes have been observed in 25 patients. In 12 of these, a primary disease of the small pulmonary vessels is described: 5 had panarteritis nodosa limited to the pulmonary vessels; 2 had endarteritis obliterans, as a part of a generalized arteritis involving the systemic circulation; 3 had multiple emboli and 1 probably had a thromboarteritis obliterans; in one a primary endophlebitis obliterans is described. In 13 other cases the arterial changes followed primary parenchymal lung disease. Posthypertensive changes are seen in most of these cases and also in 25 other observations of chronic congestion of the lung, due to mitral stenosis or other left heart disease. Posthypertensive changes are divided in 2 phases: an early phase of hypertrophy of the muscular elements of the media of the small arteries and of thickening of the elastic fibers; and the second phase of degenerative and fibrotic changes secondary to excessive thickening of the wall. Two cases are interpreted as instances of genuine (idiopathic) pulmonary hypertension.

CALABRESI

Giarelli, L.: Pathology of the Arteriovenous Anastomoses in Pulmonary Artery Sclerosis. Riv. Anat. Pat. e Onc. **10:** 719 (Dec.), 1955.

The autopsy is reported of a 22-year-old woman who had advanced pulmonary artery arteriosclerosis and marked hypertrophy of the right ventricle. Serial sections of the lungs showed: (1) obliterating endarteritis of small arteries and of the arteriovenous anastomoses, (2) anastomotic formations of unusual characteristics; (3) fibrinoid necrosis involving predominantly the arterioles and the arteriovenous anastomoses. The origin of the pulmonary artery disease and hypertension was not established. The good correlation between the vascular changes and the ventricular hypertrophy was noted; the involvement of the anastomoses in the sclerotic process was stressed.

CALABRESI

PHARMACOLOGY

Brodwall, E. K.: Atrio-ventricular Block after Gynergen. Acta. Med. Scandinav. **154:** 387, (June 9), 1956.

A patient age 47 years is described in detail. The patient was given 1 ml. of neo-gynergen for vaginal bleeding. Irregular heart action developed immediately and 10 minutes later the patient fainted. The electrocardiogram disclosed a short period of ventricular standstill and transient prolongation of the P-Q interval to 0.32 sec. Later tracings showed a P-Q interval varying from 0.20 to 0.23 sec. The patient developed generalized urticaria 30 minutes after the injection. This lasted for only 1 hour.

ROSENBAUM

Biörck, G.: The Content of Cytochrome c in Human Heart and Skeletal Muscle. Acta med. scandinav. **154:** 305 (May 26), 1956.

The author used a chromatographic method, that of Loftfield and Bonnichsen, to determine the cytochrome c content of human heart and skeletal muscle from adults, children and fetuses. The level in the left ventricular muscle of adults averaged 47 mg. per 100 Gm. of dry muscle whereas, in abdominal muscle the content averaged 7 mg. per 100 Gm. of dry muscle, a ratio of 7:1. The value for diaphragmatic muscle was 24 mg. per 100 Gm. of dry weight. The values varied considerably from patient to patient, especially for skeletal muscle. The levels rose with advancing age and very low contents were found in fetal hearts. Muscle from the left ventricle disclosed higher contents than did that from the right ventricle except in instances of pulmonary hypertension. In 2 analyses the cytochrome *c* content of infarcted heart muscle was only half of that obtained from a noninfarcted area of the same heart. The author concludes that there is little experimental evidence of an increase in cytochrome *c* in anoxic conditions or that cytochrome *c* is therapeutically useful in conditions of tissue anoxia.

ROSENBAUM

Sapin, S. O., Donoso, E., and Blumenthal, S.: Digoxin Dosage in Infants. Pediatrics **18:** 730 (Nov.), 1956.

The authors report a study to determine the optimum dosage of digitalis preparations for use in infants for maximum therapeutic effect. They point out the great individual variation and sensitivity to such preparations, and the difficulty of clinical assessment of optimal digitalization in infants. Fourteen infants under 6 months of age were studied carefully over a several day period with serial electrocardiograms taken at controlled times. Precordial positioning was maintained by careful gentian violet marking of the electrode placement areas. Normal variations in the electrocardiogram were determined. After the preliminary studies were done, each infant was given a calculated intramuscular dose of digoxin on the basis of body weight. Serial electrocardiograms were determined every 3 to 5 days thereafter for a period of 3 weeks. Following this initial study, increasing dosages of digoxin were given to each infant. Vomiting was taken as an end point for the beginning of toxicity. The electrocardiograms were analyzed to determine whether any changes appeared in measurements of the rate, P-R interval, Q-T interval, elevation or depression of the S-T segment, and height of the T wave after the various dosages of drug had been given. In addition, 15 infants with congenital heart disease, which resulted in congestive heart failure, were studied by electrocardiograms after various digitalizing dosages. From an analysis of the data obtained the authors recommend that infants in need of digitalis be given 75 μg. per Kg. of body weight of digoxin in a 24-hour period as an initial digitalizing dose, either orally or intramuscularly. If the desired effect is obtained, a maintenance dose of 25 μg. per Kg. of body weight should be given daily. If the desired effect is not obtained after the initial dose, 25 μg. per Kg. should be given every 6 to 8 hours, depending upon the severity of the failure, until satisfactory effect is achieved or toxic signs appear. The authors consider changes in the S-T segment or T wave to be normal and not a sign of toxicity. The authors point out that relatively large amounts of digoxin might be required by some infants for initial digitalization and maintenance.

HARVEY

Zapata-Ortiz, V., and Stastny, P.: Action of Chlorpromazine in Experimental Hemorrhagic Shock. Arch. int. pharmacodyn. **107:** 431 (Sept.), 1956.

Hemorrhagic shock was produced in 72 dogs by bleeding sufficient to lower the arterial pressure to 20 mm. Hg and maintaining this depressed level for 2½ hours. The animals were divided in 4 groups: 20 were used as controls and were reinfused at the end of the stated interval; 22 dogs received chlorpromazine, in doses ranging from 1.5 to 5.0 mg. per Kg., before bleeding; 15 received the drug 75 minutes after the onset of hypotension; 15 were given chlorpromazine at the end of the experiment. The animals were observed for 24 hours. Twenty of the 22 controls died in a state of shock; 15 of those receiving preventive chlorpromazine administration survived the prolonged hypotension; also in the 2 groups receiving "curative" treatment, the percentage of survivals was higher than in the control group. Investigations of vasoactive materials in serum were reported; although they have verified some of the observations of Shorr and Zweifach, and presented suggestive evidence that chlorpromazine hinders production or favors inactivation of vasodepressor material, the authors do not adopt the view that this material is the proved decisive factor in shock. The mechanism of action of chlorpromazine remains obscure. Since dibenamine is effective in the prevention but ineffective in the treatment of hemorrhagic shock, it seems improbable that the 2 drugs have a common mechanism of action.

CALABRESI

Luduena, F. P., Howard, J. W., and Borland, J. K.: The Effect of Local Anesthetics on the Refractory Period of Rabbit Isolated Auricle. Arch. intnat. pharmacodyn. **107:** 335 (Sept.), 1956.

The effect of quinidine and of procaine on the maximal rate of stimulation of the isolated rabbit atrium was compared with the effect of a series of procaine and thiocaine derivatives known to have high local anesthetic potency. The relationship between this effect, used as a measure of the refractory period, and their local anesthetic potency, and also

their toxicity, was presented. A highly significant correlation was found between the effect of these compounds on the refractory period of the atrium and their local anesthetic activity. A significant correlation was also found between the effect on the refractory period and the intravenous toxicity in mice. The most active of the compounds tested was approximately 350 times more active than procaine and quinidine.

CALABRESI

Göing, H., and Kempe, H. D.: The Effect of Rauwolfia Serpentina, Khelline, Camphor, and Radix Valerianae on Experimentally Produced Arrythmias. Arch. Int. Pharmacodyn. **107:** 255 (Sept.), 1956.

Cardiac arrhythmias and sensitization to strophantidine were produced in cats and guinea pigs by aconitine. Several drugs were tested for their antiheterotopic action. Reserpine and raubasine, 2 pure alkaloids from *Rauwolfia serpentina*, did not prevent arrhythmias produced by aconitine. The action of ajmaline was similar to that of quinidine. Experimental arrhythmias could be prevented or were delayed if ajmaline was given before or after aconitine. The action of aconitine was in some respect enhanced by khelline. Camphor and extracts of radix valerianae had no antiheterotopic effect. The increase in sensitivity to strophantidine by aconitine was not influenced by the drugs mentioned above.

CALABRESI

Arora, R. B., and Madan, B. R.: Pamaquin and Primaquin in Experimental Cardiac Arrhythmias. Arch. Int. Pharmacodyn. **107:** 215 (Aug.), 1956.

The antiarrhythmic effect of pamaquine naphthoate and of primaquine diphosphate was compared with the effect of quinidine in 80 adult mongrel dogs anesthetized with pentobarbital. It was found that both drugs were more effective than quinidine in acetylcholine-induced and in aconitine-induced atrial fibrillation, and also in atrial flutter due to electric stimulation. Unlike quinidine, they fail to afford protection against ventricular arrhythmias induced by hydrocarbon epinephrine. In cats under dial-urethane anesthesia the effects of these drugs on the atrioventricular conduction and on the refractory period were tested by measuring the P-Q and the Q-T interval respectively; both primaquine and pamaquine produced greater prolongation of these intervals than quinidine.

CALABRESI

Rapela, C. E.: Differential Secretion of Adrenaline and Noradrenaline. Acta. physiol. latinoamericana **6:** 1 (No. 1), 1956.

The concentration of epinephrine and norepinephrine of the adrenal venous blood was measured in dogs by comparing the effects of the plasma on the rat uterus during diestrous and on the arterial blood pressures of the dog, according to Gaddum and Lembeck. Dogs with severed vagi, in artificial respiration, under chloralose or nembutal anesthesia, and on heparin were used. Asphyxia increased 40 times the adrenal medullary secretion, without changes in the proportion of the 2 hormones. The section of the greater splanchnic nerve decreased the adrenal medullary secretion and the proportion of epinephrine. Stimulation of the splanchnic nerve increased the medullary secretion: the proportion of the 2 amines varied with the type and intensity of the electric stimuli. The intravenous injection of nicotine increased the total secretion and the proportion of epinephrine. It was concluded that these observations support the hypothesis of preferential epinephrine or norepinephrine secretion by different cells of the adrenal medulla.

CALABRESI

Wedd, A. M., and Blair, H. A.: A Comparison of Effects of Lanatoside C and Digoxigenin on Heart Muscle. Arch. Int. Pharmacodyn. **107:** 127 (Aug.), 1956.

Comparative observations were reported on the effect of Lanatoside C and of its aglycone digoxigenin on the heart of the turtle. Spontaneously beating atria and rhythmically stimulated or spontaneously beating strips of ventricle were used as test preparations, in concentrations ranging from 1:4 million to 1:0.5 million. Both drugs had a definite vagal effect and produced a nonspecific shortening of the ventricular muscle at approximately the same rate and intensity for the first hour of action. The genin appeared to raise the threshold of electric stimulation more promptly and to a greater degree. Genin often produced ventricular tachycardia early in its action and at comparatively low concentrations. The shortening of systole and of the refractory period of the ventricular muscle characteristic of the glycoside was a negligible effect of the genin. The sugar moiety appeared to act as an integral part of the molecule and not merely to prolong or intensify the action of the phenanthrene nucleus. The compounds were handled differently by the myocardium; early reversal of the genin action was noted.

CALABRESI

Duff, R. S., and Ginsburg, J.: Antagonism Between Chlorpromazine and Noradrenaline in Blood Vessels of the Hands. Brit. J. Pharmacol. **11:** 318 (Sept.), 1956.

The infusion of chlorpromazine into the brachial artery caused a marked reduction in the constrictor response in the hand to norepinephrine. When the response to norepinephrine is expressed as the percentage reduction in hand blood flow (82 per cent before and 27 per cent after chlorpromazine), the inhibitory effect of chlorpromazine is significant. The resting level of flow was of course higher after

the infusion of chlorpromazine alone. The reduction of norepinephrine vasoconstriction must, therefore, be partly attributed to the direct dilator action of chlorpromazine, probably involving the sympathetic nerve endings in the vessel walls.

AVIADO

Mohme-Lundholm, E.: Effect of Adrenaline, Noradrenaline, Isopropyl-Noradrenaline and Ephedrine on Tone and Lactic Acid Formation in Bovine Tracheal Muscle. Acta. physiol. scandinav. **37:** 1 (July 17), 1956.

Four drugs, which are among the principal symptomatic agents used in bronchial asthma, all had a relaxing and a lactic acid forming effect on the tracheal smooth muscle. The degree of relaxation tended to run parallel with the rise in lactic acid content. Drugs inhibiting glycolysis totally abolished the relaxing effect of all these sympathomimetic amines.

AVIADO

Ells, H. A., Caputto, R., and Furman, R. H.: Metabolic Properties of Quinidine; Effects of Quinidine Sulfate on Anaerobic Carbohydrate Metabolism of Rat Diaphragm. Proc. Soc. Exper. Biol. & Med. **93:** 189 (Nov.), 1956.

Quinidine inhibits the uptake of added glucose and fructose by rat diaphragm under anaerobic conditions and abolishes the stimulation of glycolysis by glucose and fructose. It is suggested that the inhibition of glucose uptake happens prior to the step at which sugars and glycogen share a common metabolic pathway. Such an action may account for the decrease in human glucose tolerance noted by Furman and Howard following quinidine administration.

AVIADO

Hutcheon, D. E., Scriabine, A., and Morris, D. L.: Cardiovascular Action of Hydroxyzine (Atarax). J. Pharmacol. & Exper. Therap. **118:** 451 (Dec.), 1956.

This tranquilizing drug caused a transient fall in arterial blood pressure in anesthetized cats. It also reduced the incidence and duration of ventricular arrhythmias induced by epinephrine and harman methosulfate (a profibrillatory agent). Hydroxyzine appeared to block selectively this effect of epinephrine without affecting its stimulant action on the force and rate of cardiac contractions. Similar antifibrillatory properties have been previously reported by Finkelstein for chlorpromazine.

AVIADO

Cosmides, G. J., Miya, T. A., and Carr, C. J.: A Study of the Effects of Certain Lactones on Digitoxin Toxicity. J. Pharmacol. & Exper. Therap. **118:** 286 (Nov.), 1956.

Lactones (tetrahydrofurfuryl alcohol and butyrolactone) protected chicken embryos, frog's heart and dog's heart from digitoxin toxicity. The results appear to support the theory that the unsaturated lactone of digitoxin is essential for cardiotonic activity and toxicity and that a chemically related structure (another lactone) may compete for the same receptor to antagonize its action on the myocardium. The lactones probably act by blocking the following postulated effects of digitoxin: inhibition of aerobic phosphorylation and inhibitory effects on adenosinetriphosphatase and cholinesterase of the heart.

AVIADO

Rose, J. C., and Lazaro, E. J.: The Extracardiac Hypotensive Effect of Veratrum. J. Pharmacol. & Exper. Therap. **117:** 461 (Aug.), 1956.

When administered to dogs maintained with a mechanical left ventricle of constant output, the veratrum alkaloids produced a hypotensive response. This indicates that the induced hypotension occurs independently of any alteration in cardiac function and is due to systemic vasodilation. The vasodilatation is initiated by the stimulation of receptors in the heart and lungs.

AVIADO

Virno, M., Gertner, S. B., and Bovet, D.: Action of Histamine on the Jugular Venous Pressure and Cerebral Circulation of the Dog. Effects of Antihistaminic Drugs (Pyrilamine and Chlorpheniramine) and a Histamine Liberating Agent (48/80 B.W.). J. Pharmacol. & Exper. Therap. **118:** 63 (Sept.), 1956.

Histamine in small doses of 0.1 to 1.0 μg./Kg. produced a transient venous hypertension sometimes accompanied by arterial hypotension. These effects are simulated by histamine liberating agents (compound 48/80) and antagonized by pyrilamine and chlorpheniramine. These results confirm those of other investigators and suggest that histamine, through its local action, may play a role in the physiologic and pathologic regulation of the cerebral circulation.

AVIADO

Lape, H. E., and Hoppe, J. O.: The Use of Serial Carotid Occlusion, Nictitating Membrane and Cross-Circulation Technics in the Investigation of the Central Hypotensive Activity of Ganglionic-Blocking Agents. J. Pharmacol. & Exper. Therap. **116:** 453 (Apr.), 1956.

The injection of tetraethylammonium bromide (TEA) into the head circulation of anesthetized dogs caused an abrupt, transient fall in blood pressure. This cross-circulation data indicate that a central mechanism is also involved in the hypotensive action of TEA and that the central site of action may be at the level of the vasomotor "center," although the data do not necessarily exclude intermediate synapses within the spinal cord. The sensitivity of

sympathetic ganglia, as compared to that of "central" area, is different between dogs and cats. Because of species differences, it is not known whether or not such a central action is important in human beings.

AVIADO

Uhle, F. C., Mitman, B. A., and Krayer, O.: Synthetic Esters of Dimethylaminoethanol Exhibiting Positive Inotropic Cardiac Activity. J. Pharmacol. & Exper. Therap. **116:** 444 (Apr.), 1956.

The erythrophleum alkaloids, and a series of closely related synthetic alkanolamine esters, were studied as to their ability to improve the volume work capacity of the isolated, failing mammalian heart. The esters derived from succinic, glutaric, adipic, and pimelic acids were found to display a positive inotropic activity of the order of 5 to 10 times that characteristic of the parent alkanolamine, dimethylaminoethanol. The results provide another manifestation of the rather extraordinary role played by the ester linkage among pharmacodynamic agents of the most diverse types.

AVIADO

Moyer, J. H., McConn, R. G., Seibert, R. A., Dennis, E. W., and Hughes, W.: A Comparative Study of Mersoben, Mercuhydrin (Parenteral Diuretics), Neohydrin and Diamox (Oral Diuretics). J. Chron. Dis. **2:** 670 (Dec.), 1955.

A study, conducted in an outpatient cardiac clinic, was made on the dosage response to 4 diuretics as measured by weight reduction in 11 ambulatory patients with heart failure. The diuretics studied were Mersoben (SU-1775) and Mercuhydrin, administered parenterally, and Neohydrin and Diamox, administered orally. The drugs were administered over a 2-day period at weekly intervals.

Mersoben, which contains 40 mg. Hg per cm.^{3}, was a more potent diuretic than equal amounts of Mercuhydrin, which also contains 40 mg. Hg per cm.^{3} The mean weight loss from both diuretics increased as the daily dose increased from 0.5 to 2.0 ml.

The dosage response curve of Neohydrin administered orally approached the diuretic response curve of Mercuhydrin and Mersoben, when adequate doses of Neohydrin (8 tablets or more per day) were given for 2 days. All were more potent than doses of 500 to 2000 mg. of Diamox given daily for an equal period of time. In no instance was the diuretic effect of any of the drugs maintained 5 days after discontinuation of the drug.

Minor reversible toxicities to all the diuretics were noted in some patients. Of the 4 drugs studied, it was suggested that Neohydrin was the oral diuretic of choice, and Mersoben the superior parenteral diuretic for treatment of patients with moderate to severe congestive failure.

MAXWELL

Nash, C. B., Davis, F., and Woodbury, R. A.: Cardiovascular Effects of Anesthetic Doses of Pentobarbital Sodium. Am. J. Physiol. **185:** 107 (Apr.), 1956.

Cardiac output fell during the first 2 to 3 hours of continuous pentobarbital anesthesia. Mean blood pressure was not much changed except during induction. Although the hematocrit value decreased during the first hour there was a slow incomplete recovery in the subsequent hours. Plasma proteins decreased in concentration and absolute amounts but plasma volume was slightly increased. The authors express the opinion that 30 mg. per Kg. is too high a dose and will induce greater changes than observed in this study. Maximum fall in cardiac output exceeded 44 per cent of control values. This effect may depend on cardiac depression.

OPPENHEIMER

Cummings, J. R., and Hays, H. W.: Cardiovascular Studies of Adrenergic and Ganglionic Stimulating Drugs Administered During Cyclopropane. Anesthesiology **17:** 314 (Mar.), 1956.

The authors investigated some of the cardiovascular effects of 13 adrenergic compounds and 2 ganglionic-stimulating agents in dogs under Stage III, plane 2, cyclopropane anesthesia. The minimal amount of epinephrine necessary to induce ventricular arrhythmias under such conditions was determined. With ether as the anesthetic agent, a 10-fold increase in this dose of epinephrine did not induce arrhythmias, thus clearly indicating the important role played by the anesthetic agent in the production of epinephrine-induced arrhythmias.

Multiple ventricular extrasystoles were found with repeated injections of epinephrine, levarterenol, isopropylnorepinephrine, nicotine, and DMPP. Although arrhythmias always appeared after the first injection of ephedrine and desoxyephedrine, subsequent administration of these drugs resulted in tachyphylaxis, as evidenced by diminution of the blood pressure response and failure of arrhythmias to develop. Initial injections of mephenteramine, methylaminoheptane, and methylaminoheptanol usually produced ventricular extrasystoles. With repeated injections of these compounds slowly developing tachyphylaxis appeared. With phenylephrine, methoxamine, and naphazaline in amounts sufficient to induce a vasopressor response equal to that of an arrhythmia-dose of epinephrine, the cardiac rhythm was unaffected.

The results of this study indicate that the drugs that induce ventricular arrhythmias in a myocardium sensitized by cyclopropane may do so by increasing the force of cardiac contraction.

SAGALL

Ford, R. V., Madison, J. C., and Moyer, J. H.: Pharmacology of Mecamylamine. Am. J. M. Sc. **232:** 129 (Aug.), 1956.

Mecamylamine is a ganglionic-blocking agent

that interrupts impulse transmission through the autonomic ganglia. Duration of ganglionic blockade has been shown to be 10 to 20 times longer than that with hexamethonium and 3 to 4 times longer than that with pentolinium. In this report, the pharmacologic effects of the drug in experimental animals and human hypertensive subjects are presented. In animals, the drug blocked the hypertensive response following carotid occlusion; similarly, blockade of the hypertensive effect of distal vagal stimulation was produced. The renal hemodynamic response to the drug revealed a decrease of glomerular filtration rates to 76 per cent of control; a similar decrease in renal blood flow and sodium excretion was noted. The clinical observations revealed rapid and complete absorption of the drug. There was a calculated mean pressure reduction from 149 to 95 after drug administration with an average onset of 68 minutes and an average duration of 17 hours. The average dose was 13.5 mg. in this group of patients. Renal studies disclosed slight decreases in renal plasma flow and glomerular filtration rates. In the tilted position after administration of the drug, blood pressure decline was associated with a reduction in renal hemodynamics. As a result of these studies, the authors suggest that mecamylamine is the drug of choice in the treatment of moderate to severe hypertensive patients.

SHUMAN

Murtha, E. F., Stabile, D. E., and Wills, J. H.: Some Pharmacological Effects of N-Propyl Nitrate. J. Pharmacol. & Exp. Therap. **118:** 77 (Sept.), 1956.

The hypotension that occurs immediately following poisoning from propyl nitrate could be associated with a direct effect on vascular smooth muscle and a direct depression of cardiac muscle. The latter was demonstrated by depression of the isolated rabbit heart and of the dog heart contractile force. Transient apnea followed by hyperpnea, abnormal electrocardiogram and moderate methemoglobinemia also occurred. The hemodynamic effects are similar to those of nitrites and nitrates used clinically.

AVIADO

Innes, I. R., Kosterlitz, H. W., and Krayer, O.: Studies on Veratrum Alkaloids. XXIV. The Inhibition by Veratramine and Veratrosine of the Cardioaccelerator Effect of Electrical Stimulation of the Accelerator Nerves. J. Pharmacol. & Exper. Therap. **117:** 317 (July), 1956.

These 2 veratrum alkaloids injected in spinal cats were observed to lower the basal heart rate and to diminish the increase in rate due to stimulation of the accelerator nerves. Chronic sympathetic denervation of the heart did not fundamentally alter these effects. Two possible mechanisms are suggested: blockade of the pacemaker against the transmitter liberated from the accelerator nerve endings, or interference with the formation of a hypothetical substance essential for the normal activity of the sinoatrial node.

AVIADO

Brill, I. C., Burgner, P. R., and David, N. A.: Acetyl-Digitoxin (Acylanid): Rapid Digitalization and Maintenance by Oral Administration. Ann. Int. Med. **44:** 707 (Apr.), 1956.

The purpose of this study was to determine the effectiveness of oral administration of acetyl-digitoxin, which is a digitalis glycoside derived by enzymatic cleavage from lanatoside A. Twenty-six hospitalized patients were initially digitalized with this preparation and a group of 46 ambulatory patients, previously digitalized by other preparations, were placed on maintenance therapy. Because acetyl-digitoxin has a short latent period, with rapid onset of action, it was found useful for rapid digitalization; it was given in divided doses, 0.8 mg. initially, followed by 2 0.4 mg. doses given at 2-hour intervals. The results were carefully noted by clinical and electrocardiographic observations. In most cases a total of 1.6 mg. of acetyl-digitoxin effected satisfactory digitalization within 6 to 8 hours of therapy. Few toxic or untoward reactions were encountered, and such as appeared were readily reversible by discontinuing the medication for 24 to 48 hours. Nausea and vomiting, when they occurred, were generally seen within an hour or 2 of administration of a full digitalizing dose of the drug, while arrhythmias, when noted, usually occurred several hours later. Thus, the more serious toxic effects of acetyl-digitoxin may be prevented by discontinuing the drug upon the appearance of nausea and vomiting. For maintenance, an average of 0.15 mg. of acetyl-digitoxin per day was found most satisfactory.

WENDKOS

Okita, G. T., Plotz, E. J., and Davis, M. E.: Placental Transfer of Radioactive Digitoxin in Pregnant Women and Its Fetal Distribution. Circulation Research **4:** 376 (July), 1956.

Studies on the placental transfer of biosynthetically labeled C^{14}-digitoxin in 4 pregnant women indicate that less than 1 per cent of the administered drug was detected in the fetus as unchanged digitoxin and less than 3.5 per cent as its metabolic products. On a tissue-weight basis, the fetal heart and kidney had relatively higher concentrations of digitoxin than other organs. In all probability, the amount of digitoxin that crossed the human placenta may be considered to be nontoxic to the unborn child. Although the fetal heart had a higher concentration of the glycoside than the adult atrial appendage on a tissue-weight basis, the demonstration (by Wollenberger) that the immature myocardium

was more resistant to the cardiac drug than that from the adult may in part reduce this difference.

AVIADO

Maxwell, R. A., Plummer, A. J., and Osborne, M. W.: Studies with the Ganglionic Blocking Agent, Chlorisondamine Chloride in Unanesthetized and Anesthetized Dogs. Circulation Research **4:** 276 (May), 1956.

Since the introduction of ganglionic-blocking agents in the treatment of hypertension, much work has been done to develop ganglionic-blocking compounds having increased potency coupled with long duration of action. The trained, normotensive unanesthetized dog responds to such drugs by exhibiting a drop in systolic pressure, narrowing of pulse pressure, and marked tachycardia. A study of the minimal doses required to relax the nictitating membrane following oral and intravenous administration of chlorisondamine indicates that its more prolonged oral activity (as compared to hexamethonium and pentapyrrolidinium) is most likely due to its persistence in the tissues. Administration of equipotent oral doses of the 3 drugs to the same unanesthetized dog resulted in comparable systolic pressure falls but the duration of action of chlorisondamine was 4 times longer than that of the other 2.

AVIADO

Swain, H. H., Kiplinger, G. F., and Brody, T. M.: Actions of Certain Antibiotics on the Isolated Dog Heart. J. Pharmacol. & Exper. Therap. **117:** 151 (June), 1956.

All of the common antibiotics examined, with the exception of sodium penicillin, exert a negative inotropic effect upon the isolated dog heart. On a molar basis, chloramphenicol is the most potent, followed in order by chlortetracycline, oxytetracycline, and tetracycline, streptomycin and dihydrostreptomycin, and finally potassium penicillin. Actions previously attributed to penicillin represent potassium ion intoxication whereas the tetracyclines act by forming insoluble salts with calcium ion. These observations explain why cardiac toxicity is so seldom encountered clinically. Chloramphenicol is far the most potent in this regard, and several investigators have encountered instances of cardiovascular collapse.

AVIADO

Weisberg, H., and Griffith, F. R., Jr.: Similarity of Effect of "Adrenalin", Adrenaline and Nor-Adrenaline on the Cat Denervated Heart. Proc. Soc. Exper. Biol. & Med. **92:** 387 (June), 1956.

No difference could be found in the quantitative responses of the cardiac rate of the acutely denervated cat heart to epinephrine or norepinephrine. This work confirmed several reports by others that, contrary to Goldenberg's initial observation in man, epinephrine and norepinephrine affect the excitability of the heart in a quantitatively and qualitatively similar manner.

AVIADO

Deranleau, D. A., Harvey, P. A., and Meyers, F. H.: Epinephrine-Chlortetracycline Induced Arrhythmia in the Isolated Rat Heart. Proc. Soc. Exper. Biol. & Med. **92:** 843 (Aug.–Sept.), 1956.

The effect of this antibiotic on the isolated heart is practically identical with the effect of a known chelating agent, tetrasodium versenate. Since this effect can be reversed temporarily by manganese, it is postulated that chlortetracycline causes irregularities by chelation of the cofactor of cholinesterase. The cofactor may be manganese which inactivates the cholinesterase and permits acetylcholine to accumulate and to exert its inhibitory effect on the heart.

AVIADO

Maxwell, R. A., Plummer, A. J., Ross, S. D., and Osborne, M. W.: Effect of Ganglionic Blocking Agents on Pressor Responses Induced by Splanchnic Faradization. Proc. Soc. Exper. Biol. & Med. **92:** 225 (May), 1956.

Tetraethylammonium, hexamethonium, pentamethonium, and chlorisondamine did not antagonize the pressor responses induced by peripheral splanchnic faradization (in cats). This is explained by the failure of the drugs to block the ganglionic synapse beyond the splanchnic nerve, which is largely preganglionic. These findings may well help to explain previous observations that ganglion-blocking drugs do not decrease the vascular resistance of the mesenteric bed. The accompanying hypotension is primarily due to dilatation of other vascular beds.

AVIADO

Wolf, M. M., and Berne, R. M.: Coronary Vasodilator Properties of Purine and Pyrimidine Derivatives. Circulation Research **4:** 343 (May), 1956.

Adenosine and its phosphorylated derivatives are potent vasodilators but their comparative action on coronary vessels is different. Direct injections into the perfused left coronary artery of dogs showed adenosine triphosphate and adenosine diphosphate to be more potent than the monophosphate derivative and adenosine. Although an increase in myocardial oxygen consumption was observed during infusion of adenosine triphosphate, the elevation of coronary blood flow was greater than that necessary to meet the increased oxygen demand. The action is believed to be primarily on the vessel and not secondarily due to an increased metabolic rate.

AVIADO

Read, W. O., and Kelsey, F. E.: Effect of Digoxin on Cardiac Glycogen of the Rat. Proc. Soc. Exper. Biol. & Med. **92:** 863 (Aug.–Sept.), 1956.

Digoxin in a dose of 0.2 mg. per Kg. caused either no change or a slight increase in cardiac glycogen of rats. Larger and toxic doses increased all fractions of cardiac glycogen, which can be explained by observations that high concentrations of digitalis have a central vasomotor effect that implies stimulation of sympathetic nerves and release of epinephrine. Epinephrine has been shown to increase the total glycogen in the heart.

AVIADO

PHYSICAL SIGNS

Kovtunovich, G. P., and Ivashkevich, G. A.: Diagnostic Significance of Abdominal Aortic Pulsation. Klin. Med. (Moscow) **34:** 40 (Oct.), 1956.

Of 1,206 practically healthy persons, pulsation of the abdominal aorta at the umbilical level could be palpated in 99.3 per cent, if the patient was on a hard couch and additional pressure was exerted upon the palpating hand with the other hand. At the level of the tenth rib it could be palpated in 96.8 per cent. Of 344 patients with abdominal pathology, absence of pulsation was especially common in acute pancreatitis, ileus, perforation of duodenal ulcers, and in enlargement of the retroperitoneal lymph nodes due to metastatic carcinoma and lymphogranulomatosis.

LEPESCHKIN

PHYSIOLOGY

Weil, M. H., MacLean, L. D., Visscher, M. B., and Spink, W. W.: Studies on the Circulatory Changes in the Dog Produced by Endotoxin from Gram-Negative Microorganisms. J. Clin. Invest. **35:** 1191 (Nov.), 1956.

Hypotension may occur in patients with bacteremia, associated with the liberation of endotoxin from gram-negative microorganisms. In this study of the hemodynamic events found in this condition, purified endotoxin derived from *Escherichia coli* or *Brucella melitensis* was used. The material was administered intravenously into anesthetized dogs. A sharp fall in arterial pressure was accompanied by a rise in portal vein pressure but a fall in systemic venous pressure. The hypotension was due to a fall in cardiac output. There was no evidence that pooling occurred or that myocardial failure was involved. It was suggested by the authors that localized venous spasm in the hepatic venous system, and possibly elsewhere, produces pooling of large quantities of blood. With the reduction in venous return, there is a fall in cardiac output and in arterial pressure.

WAIFE

Mellerowicz, H., and Peterman, A.: Studies on the Arterial Pulse Wave Velocity in the Aorta in Physically Trained Persons of Different Age Groups. Ztschr. Kreislaufforsch. **45:** 716 (Sept.), 1956.

The pulse wave velocity in the aorta, determined from the time difference between the carotid and the femoral arterial pulse in 200 athletes, increased from 5.9 mm./sec. in the age group of 20 to 30 to 7.6 mm./sec. in the group of 60–80. Compared to normal nonathletes, these values are considerably lower in the age groups above 50. This difference was attributed to a lower module of elasticity of the aorta, which may be either a direct cause of training or due to selection. Although the blood vessels of athletes were subjected to greater stress a few hours a day, the more economic condition of the circulation during the remaining period apparently counteracted the fatigue of the arterial elastic fibers.

LEPESCHKIN

Emmrich, J., Klepzig, H., and Reindell, H.: Clinical Significance of Subdividing the Tension Period of the Left Ventricle into the Periods of Changing Shape and Rising Pressure. Arch. Kreislaufforsch. **24:** 177 (Aug.), 1956.

The tension or isometric contraction period was determined by measuring the interval from the beginning of QRS in the electrocardiogram (lead V_5) to the nadir of the incisura in the carotid pulse, and subtracting from it the conduction time from the heart, estimated from the time difference between the incisura and the second heart sound (methods of Blumberger and Maass) or between the carotid and femoral pulses (method of Reindell). The differences between the methods did not exceed 0.023 second. The interval between the beginning of QRS and the first heart sound was considered as the period of changing shape, while the remaining part of the tension period was considered as the period of rising pressure. In 20 normal persons the tension period was 0.09 (0.072–0.107) second while its 2 components were 0.050 (0.036–0.061) and 0.040 (0.016–0.067) second respectively. In 10 athletes the average values were 0.058 and 0.048 second respectively, while in 20 patients with hypertension they were 0.058 and 0.036 for those without heart failure and 0.056 and 0.053 second respectively for those with heart failure. In 3 individuals norepinephrine caused bradycardia, elevation of both systolic and diastolic pressures and of the period of rising pressure, whereas the period of changing shape decreased and the total tension period increased slightly. In 8 individuals in the upright position the heart rate and diastolic pressure rose and the tension period increased, but the period of changing shape showed little change. In 2 individuals compression of an arteriovenous aneurysm caused decrease in heart rate and the period of changing shape, while the diastolic pressure, the tension period, and the period of rising pressure increased. When all the data on 50 individuals were plotted against the heart rate, stroke volume, diastolic pressure, and peripheral and elastic resistance, the period of rising pressure showed no relation to any of these variables except

the diastolic pressure and the stroke volume: it had a slight direct relation to the former and an inconstant inverse relation to the latter.

LEPESCHKIN

Lirman, A. V.: The Mechanism of the Paradoxical Intracardiac Conduction Disturbance (Wolff-Parkinson-White Syndrome). Klin. med. **34:** 60 (May), 1956.

Of 27 patients showing this syndrome, 25 were men; more than one half were between 20 and 23 years of age; the remainder were under 46. Fourteen had cardiovascular neurosis, 2 had initial hypertension, 2 thyrotoxicosis, 2 gastric ulcer, 1 encephalitis, 1 meningitis, and in 4 the syndrome appeared after cerebral contusion. A nervous factor was present in all patients. In an otherwise normal young man paroxysmal tachycardia appeared after, and could be induced by, epinephrine. The first electrocardiogram showed short P-R intervals and wide QRS complexes with only slightly slurred R and wide S waves; the second tracing showed a normal P-R interval, narrow QRS complexes without S waves, at the same heart rate. In an attempt to reproduce the syndrome experimentally, different branches of the sympathetic nerves were stimulated in 38 dogs. Only stimulation of the left lower outer branch consistently caused shortening of the P-R interval and widening of the QRS complexes to appear progressively after a latent period of 10 to 20 seconds; in this case the wide QRS complex was directed upward in lead II, resembling right bundle-branch block. Similar complexes, directed downward in lead II and resembling left bundle-branch block, appeared less constantly after stimulation of the third inner branch on the left side. It was concluded that sympathetic stimulation plays an important role in the genesis of the syndrome.

LEPESCHKIN

Piva, G., and Zingoni, U.: The Bainbridge Reflex. Arch. Fisiol. **56:** 71 (May 15), 1956.

The effects of injections of heparinized blood and of Ringer solution in the superior vena cava at the cardiac orifice were investigated in 20 dogs anesthetized with chloralose or with ether-chloroform and morphine. In some animals an arteriovenous anastomosis was established by connecting the left carotid artery with the catheter introduced into the vena cava. In some animals the carotid sinus was denervated bilaterally; the aortic chemoreceptors were inactivated by local injection of acetic acid. It was found that the injection of blood in quantity and at velocity sufficient to cause an increase in venous pressure had more frequently a negative than a positive chronotropic effect. These results could not be consistently interpreted by reference to the initial heart rate. The positive chronotropic effect of injections of Ringer solution might result from stimulation of the aortic chemoreceptor. In view of these results, the meaning and even the existence of the Bainbridge reflex remain questionable.

CALABRESI

Heidenreich, O., and Schmidt, L.: The Effect of Vagal Stimulation and of Clamping of the Carotid on Coronary Flow. Pflüger's Arch. **263:** 315 (Sept. 30), 1956.

In 19 experiments in dogs the blood flow in the anterior descendens branch of the left coronary artery was measured by a bubble flowmeter. In 6 experiments the coronary received blood from the carotid artery of the same animal and therefore the infusion was dependent on the prevailing blood pressure. In 13 experiments blood obtained from a donor dog was infused at constant pressure. In this group of experiments, a short stimulation of the peripheral vagus caused an increase in coronary flow; in the first group of animals this effect was masked by a fall in blood pressure. Prolonged vagal stimulation caused an opposite effect. These changes in coronary flow were inhibited by adequate doses of atropine. Stimulation of the central vagus or suppression of the carotid sinus reflex increased the coronary flow. This effect was not influenced by atropine, regitine, or vagotomy, and was interpreted as a result of increased cardiac work.

CALABRESI

Hild, R., Mechelke, K., and Nusser, E.: On the Pressure-Flow Relationship in the Arteria Pulmonalis and on the Work of the Right Ventricle in "Non-affected" Circulation and in Oligemic Shock. Pflüger's Arch. **263:** 401 (Oct. 16), 1956.

In 12 cats the pulmonary flow was measured by a density flowmeter; the pulmonary artery pressure was measured in the outflow tube of the flowmeter; pressures were also measured in the right and in the left atrium. Changes in the systemic blood pressure not causing shock or other drastic changes were obtained by small bleedings and retransfusions. Oligemic shock was produced by bloodletting, sufficient to lower the carotid artery pressure to 40 mm. Hg; this level was maintained for 15 minutes, then graded retransfusions were made. From the measurements the following data were obtained; mean pulmonary artery pressure; effective gradient between pulmonary artery and left atrium; right ventricular work (static); resistance to flow, according to Green; relative diameter, according to Wezler. The pressure-flow relationship of the pulmonary artery at varying pressure levels in the systemic circulation, was a straight line both in "non-affected" circulation and in shock; in the state of shock the line was displaced to the left, due to the lower values of flow and pressure. Also the relationship pulmonary artery-left atrial pressure followed a straight line. The efficiency of the right ventricle in oligemic shock was decreased, as expressed by the decrease in pulmonary pressure and flow with in-

creased right atrial pressure after retransfusion. The resistance to flow was increased in oligemic shock; the relative vascular diameter varied in the opposite direction. The pulse rate decreased with increase in blood volume; it was however lower in oligemic shock.

CALABRESI

Klensch, H., and Eger W.: A New Method for Physical Measurement of the Stroke Volume. Pflüger's Arch. **263:** 459 (Oct. 16), 1956.

A method for the measurement of cardiac output was presented; reference was made to a new ballistocardiographic instrument previously described. The stroke volume was estimated from the elongation ballistocardiographic curve. The assumption was made that the mean displacement of the point of gravity of the blood ejected in systole could be simply estimated from the length of the body of the subject. The law of Newton was then applied. Calculation in one case was presented.

CALABRESI

Trautwein, W., and Dudel, J.: Action Potential and Contraction of the Cardiac Muscle in Oxygen Deficiency. Pflüger Arch. **263:** 23 (Aug. 13), 1956.

The action potential and the contraction of the cat papillary muscle were recorded synchronously; the effect of varying the tension of oxygen in the bath solution was also studied. In low oxygen tension the action potential became shorter; later the amplitude was also reduced; both these effects were reversible and were followed by an overshooting when the amplitude of systole decreased rapidly; it declined further more slowly if the hypoxia was prolonged; this change was slowly reversible. The duration of systole was also shorter, and diastole was greatly prolonged; this change was readily reversible. By increasing the heart rate, when systoles were of lower amplitude, the staircase phenomenon was observed. This suggested that the effect of low oxygen tension was not due simply to reduction of available energy. There was no direct relation between the changes of action potential and of contraction.

CALABRESI.

Meesmann, W., and Schmier, J.: Oxygen Consumption of the Heart in the "Spleen-Liver Mechanism". Pflüger's Arch. **263:** 304 (Sept. 30), 1956.

Previous experiments have indicated that, after stimulation of the nerves of the spleen, the splenic venous blood improves the function of the heart; this effect is seen only if the splenic blood flows through the liver. This phenomenon has been called the "spleen-liver mechanism"; this effect is more marked on the hypoxic heart. In 12 dogs under narcosis and with the chest open, the blood flow through the right coronary artery was reduced by a clamp. The oxygen content of the arterial and of the coronary sinus blood was recorded by oxymeters; the content in oxygen and in carbon dioxide was also measured by gasometric analysis. The arterial pressure was recorded; the cardiac output had been measured in previous similar experiments. In accord with these preliminary observations it was assumed that the work of the heart was increased in the experiments here reported. The outflow of the coronary sinus was measured by a diathermy thermostromuhr. It was found that the stimulation of the splenic nerves caused a decrease in coronary flow; in 18 of 20 experiments it was found that the oxygen consumption was decreased with reference to the work of the heart; the production of carbon dioxide was also reduced. In some experiments the arteriovenous difference in lactic acid or in pyruvic acid was measured before and after the stimulation of the splenic nerves; no significant changes were found. It was concluded that, as a result of the "spleen-liver mechanism," the efficiency of the heart was increased.

CALABRESI

Giachetti, A.: Post-Tetanic Potentiation of the Heart and Effects Caused by Cholinesterase. Arch. fisiol. **55:** 407 (Dec.), 1955.

Post-tetanic poteniation has been studied in 140 isolated hearts of Bufo vulgaris and in 50 isolated hearts of guinea pigs. Mechanical or mechanical and electric effects of stimulation were recorded. It was shown that the post-tetanic effect was abolished by preliminary treatment with cholinesterase. This was taken as proof that the post-tetanic potentiation resulted from the liberation of acetylcholine. Positive and negative post-tetanic potentiation effects were described with reference to the frequency and duration of the tetanizing stimulation, to the survival time of the heart preparation, to various drugs added to the drug preparation, and to washing out and recirculation of the modified Ringer fluid used.

CALABRESI

Curri, S.R., and Tischendorf, F.: Experimental Investigations on the Histophysiology and the Histopathology of the Arteriovenous Anastomoses; in vivo Observations of the Arteriovenous Anastomoses in Normal Circulatory Conditions, during Venous Stasis, and after the Effects of Adrenalin and Histamine. Riv. Anat. Pat. e Onc. **10:** 741 (Dec.), 1955.

The arteriovenous anastomoses in the ear of rabbits was studied in vivo with normal circulation and after venous stasis or after the injection of epinephrine or histamine. Venous stasis produced opening of the anastomoses and reversal of flow. Epinephrine caused constriction, histamine caused dilatation of the anastomoses; the effect of graded

doses and the duration of the action of these drugs were reported.

CALABRESI

Burch, G. E.: Evidence for Increased Venous Tone in Chronic Congestive Heart Failure. Arch. Int. Med. **98:** 750 (Dec.), 1956.

Theoretic discussions and experimental observations are compatible with an increase in tone of the smooth muscle within the wall of the systemic veins in congestive heart failure, due in part, at least, to diffuse sympathetic nervous systemic activity. There is a need to investigate this problem further to obtain additional information to understand better the mechanisms for the venous hypertension, increase in activity of the sympathetic nervous system, and associated increase in venous tone. The relationship of the venous state to the complex physiologic, chemical, and hemodynamic phenomena in congestive heart failure, as well as alterations of these phenomena by various therapeutic procedures, also require investigation. The relationship of these changes to renal function, electrolyte and water metabolism, and other cellular and organic states must be elucidated.

It appears from experience with hexamethonium in over 100 subjects with congestive heart failure and a few experimental studies with digitalis and its derivatives that a reduction in venous pressure per se by the drugs may play a significant role in improving the clinical state. The direct cardiac effect of digitalis or the reduction of arterial blood pressure by hexamethonium is important, but its effect on venous pressure or venous tone, which may be direct or indirect, cannot be ignored. The concepts presented for the systemic venous system most probably apply as well to the pulmonary venous system in congestive heart failure.

BERNSTEIN

Cassen, B., Gutfreund, W., and Moody, M.: Demonstration of Central Nervous Mediation of Acute Pulmonary Edema Produced by Intravenously Administered Epinephrine. Proc. Soc. Exper. Biol. & Med. **93:** 251 (Nov.), 1956.

Massive doses of epinephrine administered intravenously to rats produced edematous lungs. When the spinal cord was severed (and the animal kept alive on a respirator), the same dose of epinephrine did not produce pulmonary edema. This result is interpreted as a proof of the central nervous mediation of the acute pulmonary edema produced by the administration of epinephrine. It is also postulated that the ultimate central nervous control is on precapillary sphincters. It is not possible to identify any clinical significance of the reported results because other investigators explain edema by the peripheral vascular action of epinephrine.

AVIADO

Howland, W. S., Boyan, C. P., and Schweizer, O.: Ventricular Fibrillation during Massive Blood Replacement. Am. J. Surg. **92:** 356 (Sept.), 1956.

On the basis of a study of 9 cases of ventricular fibrillation following massive blood transfusion, the authors attempted to come to some conclusion regarding the etiology of the arrhythmia. They did not believe that the speed of blood administration was the sole factor responsible for the development of this complication. They found that the injection of large amounts of citrate with the blood decreased the level of ionized calcium in the plasma, although they were unable to evaluate this change with regard to the production of ventricular fibrillation. The fact that the stored blood at the time of administration was at a low temperature was considered of possible significance, since it is known that cooling of the myocardium may lead to cardiac arrhythmias and ventricular fibrillation. The authors suggested that the use of a continuously recording electrocardiogram, the administration of calcium salts, and the replacement of blood as it is lost may all contribute to the prevention of ventricular fibrillation.

ABRAMSON

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Laake, H.: Clinical Investigation of Certain Functions of the Renal Tubules under Normal and Pathologic Conditions and under the Influence of Carbonic Anhydrase Inhibitor (Diamox). Acta med. scandinav. **155:** 27 (June 30), 1956.

In a study of normal subjects and patients with chronic renal disease such as chronic nephritis and polycystic renal disease there was an increase in ammonia excretion as the urine grew more acid but there was no correlation between the sodium and the ammonia excretion in the urine. In the normal subjects there was no correlation between urine pH and diuresis. In normal subjects the administration of Diamox was followed by a marked fall in the excretion of ammonia and titrable acids, a rise in sodium excretion and an increase in the urine pH. This depression of ammonia excretion was a lasting one. There was no response to Diamox in patients with acute or chronic nephritis. The observations here reported are considered to confirm the belief that ammonia is diffused from the cells into the lumen of the tubules and that carbonic anhydrase inhibitor renders the urine alkaline, thereby reducing the possibility for diffusion of ammonia from the cells into the alkaline medium in the urine. The resulting increase in excretion of sodium and the reduction of titrable acids results from the blockade of hydrogen ion production. The lack of response to Diamox in patients with acute and chronic renal disease is considered to be caused by damage to the

enzyme system of the kidney tissues resulting from the renal disease itself.

ROSENBAUM

Werkö, L., Bucht, H., Ek, J., and Varnauskas, E.: Studies of the Renal Circulation and Renal Function in Mitral Valvular Disease. Cardiologia **29:** 305 (No. 5), 1956.

To determine whether digitalis had a direct action on renal dynamics the effect of an intravenous injection of 0.08–1.2 mg. of Cedilanid on renal blood flow, glomerular filtration rate, and sodium excretion was studied in 20 patients with rheumatic heart disease in varying stages of compensation. Cardiac output and pulmonary and systemic pressures were determined simultaneously with the renal data. In patients in whom collection of urine for clearance tests was completed within 10 minutes after injection of digitalis, a marked and statistically significant increase in renal blood flow, filtration rate and sodium excretion could be demonstrated regardless of whether these patients were hydrated. The authors concluded that lanatoside C had an early effect on renal circulation and sodium excretion which could be separated from later occurring alterations of renal function that might be due to hemodynamic influences.

PICK

Michel, D., and Nöcker, J.: Mechanical Systole and Duration of Electrical Activity in Rats Deprived of Potassium. Pflüger's Arch. **263:** 348 (Sept. 30), 1956.

In 21 male white rats trained to swim and deprived of potassium by diet, the electrocardiogram and the duration of the mechanical systole were measured; 22 other animals served as controls. Although the serum potassium was reduced to half the normal level, no difference was found in the electrocardiogram, except for the accentuation of the U deflection in some cases. No significant changes were observed in the duration of the mechanical systole. The endurance to swimming was markedly reduced in the potassium depleted animals in proportion with the fall in serum potassium.

CALABRESI

Rudolph, A. M., Rokaw, S. N., and Barger, A. C.: Chronic Catheterization of the Renal Artery: Technic for Studying Direct Effects of Substances on Kidney Function. Proc. Soc. Exper. Biol. & Med. **93:** 323 (Nov.) 1956.

Successful bladder division and catheter implantation has been performed in 5 normal dogs and 2 dogs with right-sided congestive failure. After periods as long as 5 months, no functional or pathologic evidence of renal damage was observed. The infusion of hypertonic saline (580 mEq./L.) into 1 renal artery of a normal dog produced a 5- to 10-fold increase in sodium excretion on the injected side with no change in the control kidney. A similar infusion into the renal artery of a dog in congestive failure produced no increase in sodium excretion. This is further evidence for increased tubular reabsorption of sodium in congestive heart failure

AVIADO

Weiner, I. M., Burnett, A. E., and Rennick, B. R.: The Renal Tubular Secretion of Mersalyl (Salyrgan in the Chicken. J. Pharmacol. & Exper. Therap. **118:** 470 (Dec.), 1956.

Certain observations by others support the hypothesis that mercurial diuretics are actively secreted by the tubules of the human kidney. In the renal-portal circulation in hens, mersalyl appears to be secreted by the tubules. This interpretation is based on the assumption that an excess of material appearing in the urine from the kidney on the infused side must have traversed the ipsilateral tubular epithelium.

AVIADO

Melville, K. I., and Mazurkiewicz, I.: Actions of Potassium and Calcium on Coronary Flow and Heart Contractions with Special Reference to the Responses to Epinephrine and Norepinephrine. J. Pharmacol. & Exper. Therap. **118:** 249 (Nov.), 1956.

Injections of either potassium or calcium chloride in the isolated perfused rabbit heart induce coronary dilatation. Potassium is associated with depression of amplitude of heart contraction while calcium is associated with stimulation. Perfusion with decreased potassium ion precipitated ventricular arrhythmias more readily by epinephrine and norepinephrine. It is postulated that the cardiac effects of these amines might be initiated by some mechanism involving a "potassium-deficit" in the heart.

AVIADO

RHEUMATIC FEVER

Lendrum, B. L., and Kobrin, C.: Prevention of Recurrent Attacks of Rheumatic Fever. Problems Revealed by Long-Term Follow-Up. J.A.M.A. **162:** 13 (Sept. 1), 1956.

In 1949 a follow-up study was begun to evaluate the cardiac status of children who had participated in the Herrick House program of accelerated rehabilitation after an acute attack of rheumatic fever. At intervals starting 1 year after their discharge from Herrick House, children are reexamined for evaluation only. Data obtained on 100 children examined in 1955 showed that almost one third were no longer under medical supervision, two thirds were not receiving prophylactic medication, and adjustment problems at school and at home were not always successfully managed. It is believed that recurrences of rheumatic fever will not be prevented if one relies solely on the initiative of the individual

patient and his parents. The authors think that a method must be devised for dealing with individuals who do not carry out recommendations for medical follow-up care. Professional education must be included in the community program aimed at preventing recurrences. All who deal with rheumatic children or adults need to be informed promptly about new and important discoveries made in rheumatic fever research in order to give the best convalescent and prophylactic care. Vocational guidance is at times gravely needed. All this requires a community-wide program including a registry, follow-up program, educational program, a method of providing prophylaxis, and the necessary laboratory services.

KITCHELL

Grubschmidt, H. A.: Elements of a Rural Rheumatic Fever Program. J.A.M.A. **162:** 102 (Sept. 8), 1956.

A rheumatic fever program officially begun in February 1951 was administered by a county department of health. Funds come from both the county and state. Local medical, laboratory, clinic, and hospital facilities were utilized. The program served a widespread rural area with an approximate population in 1951 of 105,000 people. Over 550 patients passed through the clinic and of these 140 were diagnosed as inactive rheumatic fever with or without residual heart disease. About 50 were found to have congenital heart disease with or without associated rheumatic fever. In 90 patients a definitive diagnosis had not yet been made but the patients were still under observation. It was noted that during the 5 years of the program's activity, the number of patients with active rheumatic fever had diminished steadily. It was believed that this decrease in recurrence had resulted in some measure from the improvements in methods of prophylaxis. During the first 2 years of the program prophylactic methods and choice of patient were left to the discretion of the physician. As more information was obtained, penicillin, 200,000 to 400,000 units daily, was prescribed automatically unless there was sensitivity to the drug, in which case a sulfonamide was substituted. During the last year, benzathine penicillin G 200,000 units once daily was used as a prophylactic agent. The cost of the program per patient clinic visit (exclusive of hidden expenses such as physicians' services, clinic space, public health nursing, stationery, and similar items) averaged $4.64.

KITCHELL

ROENTGENOLOGY

Endrys, J., and Černohorsky, J.: The Clinical Significance of the Finding of Calcified Coronary Arteries Diagnosed by X-ray in Vivo. Cardiologia **29:** 426 (No. 6) 1956.

The authors were able to demonstrate roentgenologic calcification of the coronary arteries in 52 patients representing 0.7 per cent of all individuals examined over a period of 18 months, and 2.4 per cent of patients over 50 years of age. In 2 patients calcification of both coronary arteries was found and in 4 patients roentgenologic calcifications were confirmed by autopsy. In about half the patients, coronary disease could be established on clinical grounds, in one fourth the electrocardiogram alone was abnormal. In the rest both clinical and electrocardiographic findings were normal. However, among patients older than 65 years who revealed coronary calcifications, clinical findings were positive in 85 per cent and the electrocardiograms abnormal in the remainder. The authors recommend a systematic search for calcification of coronary arteries in routine x-ray examinations, since such a finding is an important aid in the establishment of coronary disease.

PICK

Govea, J., Aguirre, F., and Amado Ledo, E.: Tomographic Radiological Study of Mitral Stenosis. Rev. Cubana Cardiol. **17:** 1 (Mar.), 1956.

The tomographic method is the only one allowing representation of the left atrium in the anteroposterior view, as well as visualization of the left branch of the pulmonary artery and the vena azygos. It is the only method allowing direct determination of left ventricular size by means of serial sections. This is important in the diagnosis of mitral regurgitation. The authors recommend routine use of tomography in heart disease, and particularly in mitral stenosis.

LEPESCHKIN

DePass, S. W., Stein, J., Poppel, M. H., and Jacobson, H. G.: Pulmonary Congestion and Edema in Uremia. J.A.M.A. **162:** 5 (Sept. 1), 1956.

This study denies the existence of the roentgenographic entity known as "pulmonary azotemia," "uremic lung," or "uremic pneumonia." Six patients are presented showing bilaterally symmetrical densities in the central lung field with comparatively clear peripheral zones. Only 3 had uremia. All had symptoms consistent with congestive heart failure, and there was clinical evidence of increased fluid volume in each patient. It is believed that the roentgenographic findings described represent primarily pulmonary congestion and edema. Fluid retention, varying degrees of cardiac failure, often a superimposed pulmonary infection, as well as an increased respiratory rate, all enter into the formation of this picture.

KITCHELL

Hsu, I., and Kistin, A. D.: Buckling of the Great Vessels. A Clinical and Angiocardiographic Study. Arch. Int. Med. **98:** 712 (Dec.), 1956.

Sixteen patients in the present study showed quite clearly that buckling of the great vessels was a benign condition and that surgery was not indicated. Buckling was a common condition. The frequency of diagnosis depended on the interest of the observer. The buckled vessels could be demonstrated by angiocardiography and if necessary by direct carotid injection to differentiate it from aneurysm.

The clinical features of special interest in the present study were as follows: palpable left-sided buckling in the absence of its counterpart on the right side; tracheal deviation secondary to a buckled vessel; 2 buckled vessels side by side, resulting in a large pulsating mass which suggested an aneurysm; 2 instances of a buckled right internal carotid artery.

BERNSTEIN

Wilder, R. J., Moscovitz, H. L., and Ravitch, M. M.: Transventricular and Aortic Angiocardiography and Physiologic Studies in Dogs with Experimental Mitral and Aortic Insufficiency. Surgery **40:** 86 (July), 1956.

The authors attempted to evaluate the use of contrast media for visualization of the left heart chambers and aorta of dogs as a means of detecting retrograde reflux through the aortic or mitral valves. A catheter was passed retrograde from the femoral artery so as to be positioned just above the aortic valve or advanced into the apex of the left ventricle. An 18-gage needle, connected to a 20-ml. syringe, was passed percutaneously into the left ventricle. Pressure curves from the left atrium, left ventricle, and aorta were obtained through direct needle puncture. In the acute experiments, after experimental mitral insufficiency or stenosis or aortic insufficiency or stenosis had been produced, pressure and roentgenographic studies were performed. In another series, dogs with experimental valvular lesions of long standing were followed roentgenographically and with pressure pulse recordings. The authors found that mitral insufficiency was readily detected on the roentgenogram when radiopaque material was instilled into the left ventricle, the size of the atrium being clearly outlined. In this regard, the technic was believed to be unusually sensitive and detected small volumes of regurgitated material at a time when the pressure studies failed to show anything but a minimal change. On the other hand, large degrees of insufficiency were more accurately estimated through left atrial pressure curves. Free reflux of the dye into the left ventricle occurred when aortic insufficiency was present. The authors concluded that the instillation of a contrast medium into the left side of the heart can improve the precision of diagnosis in many types of congenital and acquired heart disease. However, quantitation of aortic or mitral insufficiency appears difficult.

ABRAMSON

SURGERY AND CARDIOVASCULAR DISEASE

Logan, G. A., Merendino, K. A., Bergy, G. G., and Bruce, R. A.: A Preliminary Evaluation of Transventricular Aortic Commissurotomy with an Improved Dilator. New England J. Med. **255:** 802 (Oct. 25), 1956.

Fifteen patients were subjected to aortic valve surgery by means of a modified Bailey dilator using a transventricular approach. The shaft of this dilator was only slightly more than one half the diameter and one third of the area of the original Bailey instrument, thereby requiring only a small incision for the insertion of the closed instrument into the left ventricle. Ten patients had aortic stenosis alone and 5 additional patients had associated mitral stenosis or aortic insufficiency or both. All patients were in functional classification class III or IV. There were no operative deaths but 3 patients died in subsequent weeks of congestive heart failure. Of the 12 survivors, 10 felt improved after operation, with reduction in severity of symptoms but with fatigue and dyspnea persisting as the most severe symptoms. Seven of the 12 patients improved in their functional classification. Striking improvement tended to be limited to the younger patients. Although only a single patient was able to work prior to operation, 6 patients were working full-time at nonstrenuous occupations after the surgery. There were no significant changes in the electrocardiographic or fluoroscopic abnormalities postoperatively. The physical-fitness-index score was in the normal range in only a single patient before operation but it was normal in 10 patients postoperatively. The average follow-up period in this group of patients was 6.4 months. Survivors of aortic commissurotomy tended to show greater increases in exercise tolerance and a better correlation of subjective and objective criteria of improvement than survivors of mitral commissurotomy. Failure to respond favorably to intensive medical therapy is considered a contraindication to operation. Advanced age and valvular calcification visible at fluoroscopy are relatively unfavorable prognostic signs so far as response to operation is concerned.

ROSENBAUM

Gothman, B. and Senning, A.: Cloth Tubes for Bridging Experimental Abdominal Aortic Defects. Acta chir. scandinav. **111:** 85 (Aug. 10), 1956.

Experimental aortic defects in dogs were bridged with Nylon cloth tubes in 3 dogs and Orlon cloth tubes in 9 dogs. The results were evaluated by postmortem studies in all cases except 1 in which an aortogram 520 days after grafting showed a good communication. The tube remained patent in 6 out of 12 dogs although slight thrombosis of the wall occurred in 2 of these. In 6 dogs the tube

became completely occluded by thrombus and in 2 of these there was also late rupture of the suture line. These observers noted that despite a "good femoral pulse" in 2 dogs the tube was completely occluded. Microscopic examination of the grafts disclosed a layer of connective tissue both inside and outside the cloth with an endothelial-like covering facing the lumen. The results that these observers had with Orlon and Nylon prostheses were definitely less favorable than they had with aortic homografts.

ROSENBAUM

Peniston, W. H., and Richards, V.: A Simple Circulatory Bypass System. Proc. Soc. Exper. Biol. & Med. **90:** 515 (Nov.), 1955.

Some method of total circulatory bypass is necessary to accomplish open intracardiac surgery. Ideally such a system should entail a minimum of danger to the subjects accompanied by a maximum of simplicity of working parts and operability. The use of homologous and heterologous lungs in combination with some type of mechanical pump has been shown by others to most closely approach this ideal. This is a report of experimental work with a homologous lung system that has been further simplified. The details of obtaining the lung and results on 12 experimental animals are presented.

MAXWELL

Kay, E. B., Zimmerman, H. A., Berne, R. M., Hirose, Y., Jones, R. D., and Cross, F. S.: Certain Clinical Aspects of the Use of a Pump Oxygenator. J.A.M.A. **162:** 639 (Oct. 13), 1956.

The authors report on the first 17 patients operated on with the aid of a rotating disk pump oxygenator. Three deaths occurred in this group; however, none was due to the employment of the apparatus per se. The remaining patients had a relatively uneventful recovery and it is believed that the development of this reliable pump oxygenator will help in developing new intracardiac surgical technics.

KITCHELL

Cooley, D. A., and DeBakey, M. E.: Resection of Entire Ascending Aorta in Fusiform Aneurysm Using Cardiac Bypass. J.A.M.A. **162:** 1158 (Nov. 17), 1956.

Although excisional therapy is now established as the method of choice for aneurysm of the aorta, this form of treatment for aneurysm of the ascending aorta has been limited until the present time to saccifform lesions in which the neck is relatively small. Because of the fatal consequences from even brief occlusion of the ascending aorta, no aneurysm in this anatomic location has been treated successfully by segmental aortic resection. In this 50-year-old man, the entire ascending aorta was successfully resected and a homograft replacement inserted with the aid of a temporary cardiac bypass. Although cardiac standstill occurred, resuscitation was easily accomplished, and it appears that the method is practical and relatively safe in terms of myocardial circulation.

KITCHELL

Swan, H., and Blount, S. G., Jr.: Visual Intracardiac Surgery in a Series of One Hundred Eleven Patients. J.A.M.A. **162:** 941 (Nov. 3), 1956.

The use of general hypothermia to permit cardiac surgery on the open heart in a dry field under direct vision has intrinsic unknown risks. There were 19 fatalities, 8 due to cardiac failure, 4 to thrombosis, 4 to hemorrhage, 3 to other causes. The authors believe that the optimum temperature level is in the range of 29 to 32 C. (84.2 to 89.6 F.) and that avoidance of lower temperatures largely eliminates cardiac arrhythmias and disturbances in the clotting mechanism. At this temperature the authors believe that 6 minutes of circulatory occlusion is safe and 8 should not be exceeded. Since this report was made, 19 additional patients have undergone operation without loss of life. As currently employed, open operation during hyperthermia for pulmonary valvular stenosis, aortic valvular stenosis, or atrial septal defect should present a risk of less than 5 per cent. The eminently satisfactory results of open operation in these diseases make an eloquent plea for broader adoption of open heart technics.

KITCHELL

Kay, E. B., Zimmerman, H. A., and Cross, F. S.: Direct-Vision Intracardiac Surgery for Pulmonary Stenosis. J.A.M.A. **162:** 563 (Oct. 6), 1956.

The development of the pump oxygenator not only enables the cardiac surgeon to perform operations within the open heart under direct vision more effectively, but also permits him to detect and correct additional abnormalities that might otherwise remain undetected. In the first 5 patients undergoing surgery, additional intracardiac defects were found by direct vision. These had not been recognized by careful studies preoperatively.

KITCHELL

Schein, C. J., Hoffert, P. W., and Hurwitt, E. S.: Aortic Embolectomy. A Critical Evaluation of Eleven Consecutive Cases. Surgery **39:** 950 (June), 1956.

An evaluation was made of the results of 11 aortic embolectomies. Five of the patients had rheumatic heart disease and were in atrial fibrillation. Three of these had experienced previous emboli. The remaining 6 patients had arteriosclerotic heart disease, and 3 of these had some type of atrial arrhythmia. In 10 instances the onset of symptoms was sudden and dramatic. The first symptom was severe pain either in 1 or both lower extremities or in the lower back or abdomen. All

patients exhibited coldness and mottled cyanosis of the lower extremities, with varying degrees of mottling of the anterior abdominal wall, absent femoral pulsations and marked to total impairment of motor power and sensation. Embolectomy was performed from 3 to 24 hours after onset. Three of the 11 patients survived. Specific contradictions to surgery were considered to be a moribund patient, nonsalvageable limbs, occlusion of more than 9 hours' duration and the co-existence of cerebral or mesenteric emboli. It was also pointed out, however, that the vast majority of patients treated conservatively will not survive. With regard to prognosis, the authors stated that in a patient with arteriosclerotic heart disease the presence of back pain indicates a poor outlook. Prompt surgery in the rheumatic patient without back pain was considered to be a more favorable combination.

ABRAMSON

Denman, F. R., and Hanson, H. H.: Aortic Embolectomy Following Mitral Commissurotomy. Surgery **39:** 985 (June), 1956.

The authors reviewed the literature regarding the association of aortic embolus with mitral commissurotomy and added 1 case of their own. In the latter at surgery there were no detectable thrombi in the atrial cavity or appendage. However, on the seventh postoperative day pain developed in the left lower lumbar region and back and numbness of the feet. An aortic embolectomy was done immediately, followed by the return of pulsations in both lower extremities. Because of the delay in the appearance of the embolic episode, it was thought that the thrombus had developed postoperatively, either at the split edges of the mitral valve or at the suture line in the fibrillating atrium. On this basis, the authors expressed the view that it was wise to administer anticoagulants during the immediate postoperative period following mitral valve surgery in patients with atrial fibrillation.

ABRAMSON

McAllister, F. F., and Fitzpatrick, H. F.: Constriction of the Mitral Annulus in the Correction of Certain Types of Mitral Insufficiency and as an Aid in By-passing the Left Ventricle. Surgery **40:** 54 (July), 1956.

An experimental study was made to determine the fate of the constricting ligature used to produce mitral stenosis. In addition, experiments were performed in which the ligature was used as a temporary device to trap pulmonary venous blood in an atrial reservoir from which it could be pumped into a subclavian artery, thus bypassing the left ventricle. The technic permitted successful left ventriculotomy in 9 instances. The authors stated that the type of suture they used was applicable only to those cases in which the mitral insufficiency was associated with a marked enlargement of the atrioventricular ring.

ABRAMSON

Glenn, W. W. L., Gentsch, T. O., Hume, M., and Guilfoil, P. H.: The Surgical Treatment of Mitral Insufficiency with Particular Reference to the Application of a Vertically Suspended Graft. Surgery **40:** 59 (July), 1956.

An attempt was made to utilize the vertical suspension of a cylindrical segment of Ivalon sponge between the mitral valve cusps for the treatment of mitral insufficiency. The intracardiac portion of the raw sponge was covered with autogenous pericardium or vein or homologous vein. The evaluation of the method was carried out in a series of dogs and in 3 patients. It was found that the sponge covered with inverted autogenous vein was superior to the other types of prostheses used. The ingrowth and coverage of the sponge with fibroblasts resulted in a living graft of stable size. Of the 3 patients upon whom the operation was performed, 1 died in the early postoperative period, while the other 2 showed equivocal improvement.

ABRAMSON

Silen, W., Mawdsley, D. L., Miller, E. R., and McCorkle, H. J.: The Experimental Production of a Competent Aortic Valve. Surgery **40:** 78 (July), 1956.

A method is described for the production of a valve in the descending aorta through intussusception of a segment of the wall of the vessel. The procedure was tested on 19 dogs, in 15 of whom either intussusception valvuloplasty or valvulotomy was performed, while 4 were subjected to both operations. Through the use of cineroentgenograms it was found that intussusception valvuloplasty allowed only minimal regurgitation and significantly reduced the elevated pulse pressure of aortic insufficiency.

ABRAMSON

Brown, I. W., Jr., Hewitt, W. C., Jr., Young, G., Sealy, W. C., and Harris, J. S.: A Simple, Expendable Blood Oxygen-Gas Exchanger for Use in Open Cardiac Surgery. Surgery **40:** 100 (July), 1956.

The authors describe a plastic blood oxygenator for use in extracorporeal circulation and present the results obtained with its use on dogs and on 1 patient. The exchanger consisted of a seamless bag of polyvinyl plastic containing loops of plastic tubing which served to increase the internal surface area. Two openings in the bag were used for introducing blood, anticoagulant and oxygen, while a third opening, at the top center, permitted outflow of the oxygenated blood. As the blood entered the bag, the latter was rocked back and forth to spread

the blood over the bag's internal surfaces. It was found that the plastic bag acted as an efficient and sufficiently rapid blood-gas exchanger to permit its use in a pump-oxygenator circuit.

ABRAMSON

Adler, R. H.: The Use of Pericardial Grafts with a Thrombin-Fibrinogen Coagulum in Esophageal Surgery. Surgery **39:** 906 (June), 1956.

An experimental study was performed in which topical thrombin and fibrinogen were used to make an interposed sticky coagulum for the purpose of promoting a rapid physiologic union between a graft of pericardium or parietal pleura and the esophagus. The coagulum effectively held the graft in place without sutures. After a period of 2 weeks, the graft was intimately adherent to the muscularis, taking on the appearance of a serosa. The author concluded that grafts of pericardium held in place by thrombin-fibrinogen coagulum functioned satisfactorily without untoward reaction and were effective in re-enforcing esophageal suture lines. Possible clinical application was considered.

ABRAMSON

Taber, R. E., and Lawrence, M. S.: Resection and Arterial Replacement in the Treatment of Popliteal Aneurysms. Surgery **39:** 1003 (June), 1956.

Two patients were presented to demonstrate the satisfactory employment of arterial homotransplants in the surgical treatment of popliteal aneurysms. At the time of operation the patient was placed in a semi-lateral decubitus position in order that the operated leg could be both externally rotated for the performance of femoral arteriography and internally rotated for exposure of the popliteal region. After the popliteal aneurysm was dissected free of the popliteal vein, the lesion was removed and replaced by the graft. Following operation the leg was immobilized for several weeks with a posterior molded plastic splint. A successful result was obtained in both patients.

ABRAMSON

Fisher, B., Wilde, R., Engstrom, P., and Fisher, E. R.: Experimental Reconstruction of the Aortic Bifurcation. Surgery **39:** 940 (June), 1956.

An experimental study was performed to evaluate the practicability of 2 different methods of reconstruction of the aortic bifurcation, using straight segments of aorta from young, incompletely grown dogs grafted into fully mature adult animals. The end-to-side and the Y types of reconstruction were found to be equally satisfactory. Better results were obtained using lyophilized grafts than fresh ones. The microscopic degenerative findings of grafts in place for 1 year were comparable to those observed in straight aortic grafts.

ABRAMSON

Horton, C., Campbell, F., Connar, R., Smith, A., and Pickrell, K.: The Use of Autogenous Skin Grafts to Repair Arterial Defects. An Experimental Study. Surgery **39:** 926 (June), 1956.

An experimental study was performed to evaluate the use of autogenous skin grafts for the repair of arterial defects. The dermal grafts were obtained from the abdomen of dogs and anchored in a previously created defect in the thoracic aorta. Of the 10 animals operated upon, using dermal skin with the dermal side inward, 4 died within 5 days following surgery from thrombosis at the graft site. The others were sacrificed 45 to 210 days after operation. On examination of the vessels, the patches appeared to be similar to normal aortic wall. Microscopically the wall was composed of tough but pliable fibrous tissue, lined with endothelium. When the fatty side of the skin graft was placed inward, the grafts also survived and functioned normally. However, when tubular dermal skin grafts were used to replace circumferential segments of aorta and the dermal surface were inward, all became thrombosed. Better results were obtained using the tubular dermal skin grafts with the fatty surface inward. The authors concluded that autogenous dermal substitutes for aorta wall appear to survive and be reinforced by a secondary layer of fibrous tissues. Therefore further study of possible clinical application in vascular surgery would seem to be indicated.

ABRAMSON

VALVULAR HEART DISEASE

Gorlin, R., and Case, R. B.: Clinical Diagnosis of Aortic-Valve Disease. New England J. Med. **255:** 368 (Aug. 23), 1956.

A correlation was made of the anatomic findings and physiologic data with the clinical observations in a group of 100 patients with aortic valve disease. In pure stenosis the carotid pulse was normal or decreased in volume, had a delayed systolic peak or a plateau quality, and was almost always associated with a coarse, rough systolic thrill felt best in the sitting position and over the left carotid artery and enhanced by expiration. When significant aortic regurgitation was present the carotid pulse was more full and quick to the touch, it had a bisferious quality in systole and a collapsing quality in diastole, and a fine systolic purr in addition to the coarse thrill of stenosis. Because the intensity of the murmur was closely related to the velocity of blood flow through the valve as well as to the valve shape and size, the murmur was very faint or even absent in isolated, severe aortic stenosis if there was also a low cardiac output. The quality of the systolic murmur bore no necessary relation to the severity of aortic stenosis, and the intensity of the diastolic murmur of insufficiency bore no close relation to the degree of regurgitation present. A decreased

aortic second sound usually meant poor valvular mobility but not necessarily predominant aortic stenosis. Poststenotic dilation of the first portion of the aorta suggested aortic stenosis, whereas predominant aortic insufficiency was usually associated with prominence of the aortic knob and descending aorta. Although valvular calcification observed radioscopically usually meant marked valvular deformity, it did not necessarily indicate stenosis as the predominant lesion. In the absence of regurgitation, a severe degree of aortic stenosis was present when the cross-sectioned area of the valve was reduced to 0.5 cm.^{2} or 15 per cent of the normal orifice size. When in aortic insufficiency there was a valvular defect during closure of 0.3 cm.^{2} or more, significant regurgitation with leaks of as much as 3 times the systemic cardiac output occurred. Electrocardiographic evidence of left ventricular hypertrophy, left bundle-branch block or delayed intrinsicoid deflection over the left ventricle occurred in 85 per cent of the patients with severe stenosis but in 15 per cent of such patients no electrocardiographic abnormality was present. The combination of electrocardiographic evidence of left ventricular hypertrophy and a normal-sized heart was strongly suggestive of pure tight stenosis.

ROSENBAUM

Wade, E. G., MacKinnon, J., and Vickers, C. F. H.: The Nature of the Increased Pulmonary Vascular Resistance in Mitral Stenosis. Brit. Heart J. **18:** 458 (Oct.), 1956.

The authors report the effects of hexamethonium bromide and atropine on the increased pulmonary vascular resistance in mitral stenosis. Atropine produced no consistent effect upon pulmonary vascular pressures, resistances or cardiac output. Hexamethonium produced a fall in resting mean pulmonary arterial pressure in 7, a rise in 1 and no change in 3. Exercise caused the pressure to rise but less so in 6 than before administering the drug. Resting total pulmonary resistance fell in 5, rose in 3 and remained unchanged in 2. Effort increased the resistance. The pulmonary capillary venous (PCV) pressure fell in 2 and rose in 1 and all 3 rose on effort. There was a relation between the pulmonary vascular resistance and the PCV pressure both at rest and on effort. The authors believe that changes in pulmonary vascular resistance following hexamethonium are limited to and dependent upon changes in the PCV pressure due to a local reflex that is not under autonomic control.

SOLOFF

Brown, J. W., Heath, D., Morris, T. L., and Whitaker, W. Tricuspid Atresia. Brit. Heart J. **18:** 499 (Oct.), 1956.

The authors describe the clinical features of 8 patients with tricuspid atresia and 1 with tricuspid stenosis, the necropsy findings in 4 and also thoroughly review the literature. All had breathlessness on exertion. The characteristic clinical findings were central cyanosis, finger clubbing, and absence of cardiac enlargement, pulmonary hypertension, and diastolic murmurs. The systolic murmur was usually maximal at the base of the heart to the left of the sternum. An abnormally prominent venous pulse was commonly present. The electrocardiogram showed left axis deviation, clockwise rotation of the heart and abnormally tall peaked P waves in lead II. There was no constant conventional radiologic appearance of the heart, but, when present, a "square" heart and diminished projection of the right cardiac border in the frontal projection were useful diagnostic features. Angiocardiography, on the other hand, was characteristic. A right to left atrial or right atrial-left ventricular shunt was usually demonstrated. Between the right atrium and the left ventricle was a characteristic clear area, the "right ventricular window." This region may become filled from the left ventricle. Cardiac catheterization may likewise demonstrate the atrial septal defect. There was, however, no indication for this study. Left ventricular and systemic blood were unsaturated with oxygen. The diagnosis was established by the demonstration of an atrial septal defect and a "right ventricular window" on angiocardiography in the cyanotic infant or child with left axis deviation in the electrocardiogram.

The prognosis was poor and the mortality higher than in any other congenital heart lesion except pulmonary atresia and transposition of the aorta and pulmonary trunk. Extensive intravascular thromboses in the muscular pulmonary arteries and veins were common in this disease. Operation, to be effective, should be carried out before changes in the small pulmonary vessels have had time to develop and is more likely to be successful when performed in infancy.

SOLOFF

Turner, R. W. D., and Fraser, H. R. L.: Mitral Valvotomy. A Progress Report. Lancet **2:** 525, 587 (Sept. 15–22), 1956.

The authors analyze the first 250 patients from the cardiac department at the Western General Hospital, Edinburgh. Of these, 9 had been followed more than 5 years, 116 more than 3 years, and 202 more than 2 years. All had been followed more than 1 year. 29 were over 50 years of age, the greatest range of age being 16–60 years. The authors' experience indicated that a "pliant" or "diaphragmatic" valve, optimal for surgical intervention, could not be predicted reliably by the triad of loud snapping first sound, opening snap and rumbling diastolic murmur. In 37 per cent of their series there were Kerley lines, transverse striations in the lung fields on chest x-ray, best seen in the right costophrenic angle. The authors subscribe to the view that these lines represent distended lymphatics

nd are indicators of pulmonary edema. The over-ll operative mortality was 8 per cent. Only 2 leaths occurred in the last 100 cases. Seven of the atients died 1 to 39 months after operation. The uthors state the opinion that the postoperative yrexial syndrome is not rheumatic recrudescence. The syndrome is probably due to traumatic ericarditis and pleuritis resulting from the opera-ion, with accompanying systemic disturbances." The ncidence was less than 5 per cent in this series. In patients re-operation was done but an inadequate irst procedure was thought responsible for the poor esult. Mitral valve calcification was present in 27 per cent, increased with age, and was more fre-quently present in men. When present the snapping character of the first sound and the opening snap tended to be inconspicuous or absent, and the mitral systolic murmur might be loud and harsh without important mitral regurgitation. The cus-tomary methods of examination are more useful than fancy technics in diagnosing mitral regurgita-tion. With proper evaluation mitral regurgitation should not be a surprise finding at operation. "A weak or absent first heart sound or snap that cannot be attributed to a calcified or rigid mitral valve with tight mitral stenosis, a loud harsh systolic murmur, maximal at the apex and heard towards the axilla, that cannot be attributed to aortic stenosis or tricuspid incompetence, and any evidence of left ventricular hypertrophy that cannot be attributed to aortic valvular disease almost in-variably signifies an important degree of mitral incompetence."

McKusick

Alvarez Mena S., Guerra, R., Pando A., Perez Montes L., and Montenegro J.: Diagnosis of Aortic Stenosis by Left Ventricular Catheteriza-tion. Rev. Cubana Cardiol. **17:** 35 (March), 1956.

This is the first Cuban case diagnosed by trans-lumbar retrograde catheterization of the aorta. The systolic pressure gradient was 27 mm.: The sudden change in pressure indicated that the stenosis was valvular. The phonocardiogram showed a proto-systolic and mesosystolic murmur, not diamond-shaped. The electrocardiogram showed left ventricu-lar hypertrophy without the tall T waves attributed to "systolic overload."

Lepeschkin

Loogen, F., Bayer, O., Wolter, H. H., and Schaub, W.: Pathologic Physiology of Mitral Stenosis. II. Comparative Clinical and Hemodynamic Studies in 200 Patients with Pure or Predominant Mitral Stenosis. Arch. Kreislaufforsch. **24:** 45 (June), 1956.

Prominence of the pulmonary conus was slight nd rare in patients with a mean pulmonary arterial pressure under 40 mm. Hg, but marked and con-tant in those with a pressure exceeding 80 mm. Hg. The degree of left atrial enlargement was inde-pendent of the left atrial pressure (estimated from the pulmonary capillary pressure), but was much greater when mitral regurgitation was present. Roentgenologic changes in the lung fields were more common in men and in persons with a high pulmonary capillary pressure. The QRS axis was +77° when the mean pulmonary pressure was under 30 mm. Hg, +84° when it was 31 to 61 mm., +97° when it was 61 to 90 mm. and +106° when it was over 90 mm. Deviation to the left from those values indicated additional systemic hypertension or mitral regurgitation. Bundle-branch block was found only in 0.3 per cent but delayed appearance of the R wave in right precordial leads was common. "P mitrale" was found in 51 per cent and showed no relation to cardiac pressures. Atrial fibrillation or flutter was found in 5 per cent of pure mitral stenosis but in 34 per cent of those with additional regurgitation. The interval from the second heart sound to the opening snap of the mitral valve was an index of left atrial diastolic pressure and, accord-ingly, of the severity of mitral stenosis; it increased from 0.03 second at a capillary pulmonary pressure of 45 mm. Hg to 0.09 second at a pressure of 15 mm. in a series of 100 patients. Usually the interval became shorter after exercise. These values applied when the systemic systolic pressure was between 100 and 130 mm. Hg; when it was higher, the interval was slightly greater due to anticipation of the second heart sound, while with lower pressure it was slightly lower. When these values appeared at a heart rate less than 80, they indicated that commissurotomy would be beneficial. The diastolic murmur of mitral stenosis usually began immediately after the opening snap, but in patients in whom this snap appeared after a long interval the murmur might not appear until after a short silent interval; this was attributed to a lower left atrial pressure, which made a longer interval necessary until the velocity of blood flow reached the murmur stage. Absence of the murmur in the presence of a signifi-cant stenosis was found in only 1 of 600 consecutive cases, while a Graham Steell murmur was found in 20 patients. The incidence of hemoptysis showed a definite increase as the mean pulmonary arterial pressure increased. Signs of heart failure such as hepatomegaly, edema and pleural effusion were present in only 7 per cent of the patients with pure mitral stenosis, but in 30 per cent of those combined with regurgitation.

Lepeschkin

Moll, A. and Schmialek, P.: The Diagnostic and Prognostic Significance of the Electrocardio-gram in Aortic Insufficiency. Arch. Kreislauf-forsch. **24:** 227 (Aug.), 1956.

In 20 patients with pure rheumatic aortic regur-gitation, the P wave in V_1 was normal in 4 and had a wide second negative phase ("P sinistrocardiale")

in 16. In 24 similar patients complicated by mitral valvular disease, a "P sinistrocardiale" was present in 16 while a diphasic P wave in V_1 with tall initial positive and wide terminal negative phase ("P cardiale") was present in 8 persons. A normal P wave can thus practically exclude additional mitral disease, while a "P cardiale" essentially proves it. In several patients a "P sinistrocardiale" appeared with the first subjective complaints; a "P cardiale" with definite signs of heart failure. The P-R interval was prolonged in 25 of 52 patients with aortic regurgitation of rheumatic origin, but in none of 25 patients with luetic regurgitation and in none of 10 patients with regurgitation due to endocarditis lenta. The QRS duration exceeded 0.09 second in two thirds of the cases with syphilitic and one fourth of those with rheumatic regurgitation; activation delay of the right ventricle was twice as common as that of the left ventricle in combined mitral disease, but did not appear at all in pure aortic regurgitation. Right activation delay appeared predominantly in younger patients while left activation delay increased in incidence with age. Left axis deviation of the QRS complex was found in one half of the patients with rheumatic and in three fourths of those with syphilitic regurgitation. A left ventricular strain pattern was found in 55 per cent; patients who did not show it had either combined mitral and aortic disease or only a mild degree of aortic regurgitation. This pattern usually developed faster in syphilitic than in rheumatic regurgitation; in the latter it may develop rapidly during bouts of acute rheumatic fever, and was attributed to myocarditis rather than to left ventricular hypertrophy. The greatest opposition between the axes of the QRS complexes and the T waves was found in syphilitic regurgitation, where it was attributed to coronary stenosis. The changes of the T waves and S-T segments were usually most pronounced in leads with tall R waves, but in some slender persons they were seen best in leads II and III in spite of slight left axis deviation. In some patients development of mitral regurgitation was accompanied by decreased amplitude of the T wave in leads V_{1-3}. Atrial fibrillation was seen in only 2 patients with pure aortic regurgitation, and these died within a few months; when mitral disease was also present, fibrillation did not offer a poor prognosis, as it was seen in one fourth of the cases.

LEPESCHKIN

Whittembury, G., Cazorla, A., and Monge, C.: Description of the Circulatory Dynamics in the Heart and Lungs in Mitral Stenosis by Means of the Dye Dilution Technique. Acta physiol. latinoamericana **6:** 15, 1956.

A study of the hemodynamics in 20 patients with mitral stenosis, by means of the dye dilution curve, was presented. The circulation time, the cardiac index, the central volume according to Newman, the intrathoracic volume according to Hamilton and the total blood volume were measured, with reference to the normal values at sea level. The circulation time and the blood volume increased in relation to the severity of the disease; the cardiac index decreased. The central volume was also increased, parallel to the severity of the disease. Expressed as percentage of total blood volume, however, this increase was significant only in grade 3 patients. No significant variations of the intrathoracic blood volume were seen. It was concluded that no systematic increase of pulmonary blood volume occurred in mitral stenosis.

CALABRESI

VASCULAR DISEASE

Bäckman, H.: Studies on Periarteritis Nodosa with Special Reference to Cardiac and Renal Involvement and Possible Aetiological Factors. Acta med. scandinav. **154:** 441 (June 20), 1956.

Clinical and pathological observations were made in 14 patients with periarteritis nodosa encountered over a 5 year period. Two of the patients were still living at the time of this report after a follow-up of 8 years. The diagnosis was made from a right nephrectomy in 1 instance and from a biopsy done during surgery for hypertension in the other. The heart was affected in 8 patients. Persistent tachycardia, independent of fever, was a common manifestation and in 5 patients in which digitalis was used the tachycardia was refractory in all but 1. Those patients with enlarged hearts also had considerable hypertension. The vascular lesions of periarteritis found in the myocardium were of varying age, generally slight in extent and present in hearts which were normal in size as well as those which were enlarged. When the coronary arteries were involved it was the small and medium-sized arteries which were most affected. In only a single patient was there a definite history of angina pectoris and although an old myocardial infarction was present it was considered only partially due to the periarteritis nodosa. Electrocardiographic abnormalities were common but non-specific in character. The vascular and parenchymal lesions produced by this disorder in the kidneys were usually very extensive. Hypertension was observed in those patients with chronic vascular lesions of the kidney. No conclusions regarding etiology could be drawn. Only 2 patients had received sulfonamides and in only 1 of those did the disease seem directly connected with its use. One patient with pulmonary localization of the disease seemed worse during sulfonamide and penicillin treatment suggesting a possible allergic sensitization to these drugs.

ROSENBAUM

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7–9170

ASSOCIATION AWARDS PRESENTED TO PHYSICIANS AND LAYMEN

Among the honors conferred on physicians, scientists and laymen in recent months by the American Heart Association for outstanding service in advancing the Heart program and for achievement in cardiovascular research were the following:

GOLD HEART AWARDS

Recipients of the Gold Heart Awards, highest award of the Heart Association for outstanding contributions to cardiovascular medicine and to the Heart organization, were Irving S. Wright, M.D., Past President of the American Heart Association; Irving B. Hexter, Cleveland publisher; and television star Ralph Edwards.

Dr. Wright, Professor of Clinical Medicine at Cornell University Medical College, has long been an outstanding leader in both the national Association and the New York Heart Association. A member of the Board of Directors of both groups, he is also Chairman of the national Association's Publications Committee and serves on the Editorial Board of *Circulation*.

Mr. Hexter, President of the Industrial Publishing Company, Cleveland, is a Vice President and Board member of the Association. He has been Secretary of the national Association, Chairman of the Board of the Ohio State Heart Association and Chairman of the Board of Trustees of the Cleveland Area Heart Society.

A special Gold Heart Award was presented to Ralph Edwards to commemorate the tenth anniversary of his "Walking Man" radio contest which raised the funds required to launch the Association as a voluntary health agency.

LASKER AWARD

Isaac Starr, M.D., former Dean of the University of Pennsylvania School of Medicine, received the Albert Lasker Award of the American Heart Association for distinguished achievement in the field of cardiovascular research and particularly for his influence in helping to develop today's vastly changed concepts of congestive heart failure. Tribute was paid to Dr. Starr for his numerous achievements as a physiologist, pharmacologist, clinician, research scientist, teacher and, above all, as an independent thinker. He is Hartzell Research Professor of Therapeutics at the University of Pennsylvania School of Medicine and serves on the Editorial Board of *Circulation*. The award, consisting of a statuette of the *Winged Victory of Samothrace* and an honorarium of $2,500, is given annually by the Albert and Mary Lasker Foundation through the American Heart Association.

SPECIAL CITATIONS TO NOBEL PRIZE LAUREATES

Special citations also were presented to three Nobel Prize winners, André Cournand, M.D. and Dickinson Richards, M.D. of New York and, in absentia, Werner Forssmann, M.D., Germany, for catheterization of the heart and research carried out by means of catheterization.

All of the above awards were presented at the Annual Meeting and Scientific Sessions of the American Heart Association in Chicago, October 25–29.

BLAKESLEE AWARD WINNERS

Five winners of the 1957 Howard W. Blakeslee Awards of the Heart Association for outstanding reporting in the field of heart and circulatory diseases were honored at a special luncheon in New York on October 5. New advances in heart surgery were featured by four out of the five winners in the categories of national news syndicates, local newspapers, national magazines and television.

Recipients of the Blakeslee Awards, each of which includes an honorarium of $500, are as follows:

Leonard Engel, free lance writer, for a series on cardiac surgery published by the North American Newspaper Alliance.

Walter Bazar, New York Journal American, for a series on heart research and advances in treatment, including surgery, entitled, "New Hope for Your Heart."

Don Dunham, Cleveland Press, for his spot news report on the first "stopped heart" operation, performed at the Cleveland Clinic.

Steven M. Spencer, for his article in the Saturday Evening Post, "They Repair Damaged Hearts," a comprehensive review of advances in heart surgery.

"*Robert Montgomery Presents*," for the NBC-TV presentation, "The Long Way Home," a one-hour dramatization about a man who suffered a heart attack and his subsequent recovery.

WORLD CONGRESS OF CARDIOLOGY ABSTRACTS DUE BEFORE FEBRUARY

The American Heart Association will receive abstracts from those persons in the United States who wish to present papers at the Third World Congress of Cardiology to be held in Brussels, Belgium, September 14–21, 1958. Summaries of the papers, consisting of 200 typewritten words in English and a translation in French, Spanish or German, must be in the Heart Association's national office, 44 E. 23rd St., prior to February 1, 1958. Participants who reside in a country outside the United States which has no National Society of Cardiology should address abstracts and translations to the Secretary of the Congress, Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

Registration for attendance at the Third World Congress of Cardiology is open to members of the various national societies and associations engaged in the study and control of cardiovascular disease as well as to physicians and scientists residing in countries where no national society of cardiology has been established. American physicians who attended the Second World Congress in Washington (1954) will receive a pamphlet on the Third Congress and application forms. Further information on the forthcoming Congress may be obtained from the American Heart Association or from Secretary Van Dooren in Brussels.

HEART ASSOCIATION ISSUES VARICOSE VEINS BOOKLET

A new illustrated booklet, entitled, "Varicose Veins," has been published by the Association. Intended primarily for distribution by physicians to patients with this condition and their families, the booklet emphasizes that the physician should be consulted early whenever varicose veins are suspected. If the physician is seen in time, it points out, he can often ward off serious damage resulting from this condition.

Single copies of the booklet are available free of charge from the American Heart Association and local Heart Associations.

BRAZIL CARDIOLOGY CONGRESS ELECTS NEW DIRECTORS

The 1960 Inter-American Meeting of the Brazilian Congress of Cardiology will be held in Rio de Janeiro, it was announced at the 14th Brazilian Congress of Cardiology held last July 7–13. The Society elected the following new officers for the 1957–58 term: President A. de Carvalho Azevedo, M.D.; Vice President, Prof. Rubens Maciel; General Secretary, Robinson Roubach, M.D.; Treasurer, G. Strunck, M.D.; Sub-Secretary, Adão G. Mattos, M.D.

GRANTS AVAILABLE TO STUDY ASIAN FLU HEART EFFECTS

The National Advisory Heart Council has recommended that the National Heart Institute encourage research on the effects of Asian Influenza upon the cardiovascular system. National Heart Institute research grants are available on a competitive basis to investigators wishing to study the cardiovascular-renal effects of influenza.

Research grant applications will be processed as rapidly as possible. Applications may be obtained by writing to Herman E. Schmid, Jr., M.D., National Heart Institute, Bethesda 14, Md.

MEETINGS CALENDAR

November 22–23: Council for High Blood Pressure Research of the American Heart Association, Cleveland. Mrs. Jerry H. Bruner, 1689 East 115th Street, Cleveland 6, Ohio.

December 3–6: American Medical Association, Philadelphia. George F. Lull, 535 Dearborn Street, Chicago 10, Ill.

December 6–7: American Federation for Clinical Research, Eastern Section, New Haven, Conn. Franklin H. Epstein, M.D., Department of Internal Medicine, Yale University School of Medicine, 333 Cedar Street, New Haven 11, Conn.

December 10–12: Southern Surgical Association, White Sulphur Springs, W. Va. Mr. George G. Finney, 2947 St. Paul Street, Baltimore 18, Md.

January 24, 1958: American Federation for Clinical Research, Southern Section, New Orleans. Kenneth R. Crispell, M.D., Department of Internal Medicine, University Hospital, Charlottesville, Va.

January 29–30: American Federation for Clinical Research, Western Section, Carmel, California. Monte A. Greer, M.D., University of Oregon Medical School, Portland, Ore.

March 9–14: International College of Surgeons, 11th Biennial Congress, Los Angeles, Karl A. Meyer, M.D., 1516 Lake Shore Drive, Chicago 10, Ill.

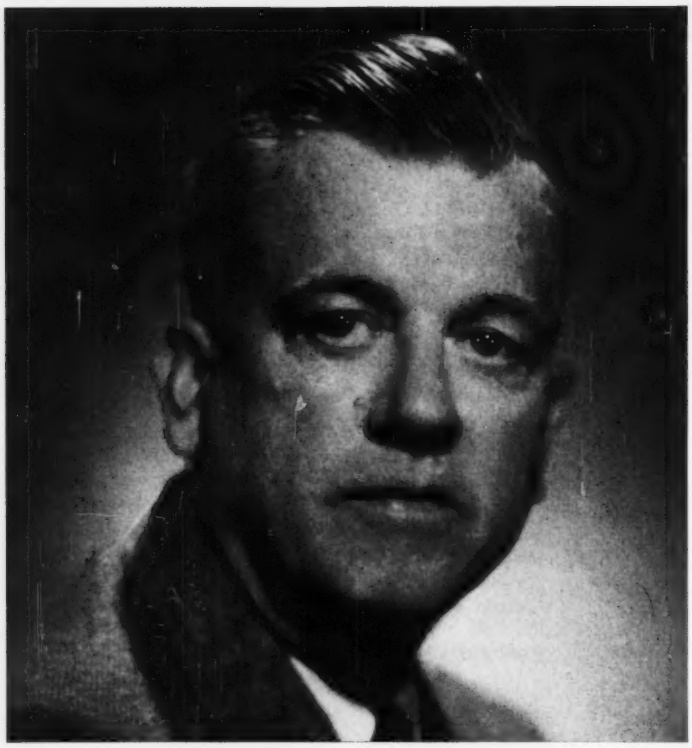
March 20–22: Chicago Heart Association, Conference on Pulmonary Circulation, Palmer House, Chicago. Wright Adams, M.D., Department of Medicine, University of Chicago, Chicago 37, Ill.

ABROAD

January 7–10, 1958: Third International Symposium on Radioactive Isotopes in Clinical Application and Research, Bad Gastein, Austria. The Second Medical Clinic, Vienna University, Vienna, Austria.

January 21–February 14: International Union of Biochemistry, General Assembly, Vienna, Austria. Prof. R. H. J. Thompson, Department of Chemical Pathology, Guy's Hospital Medical School, London, S.E. 1, England.

September 14–21, 1958: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.



EUGENE B. FERRIS, M.D., 1905–1957

With a sense of irreparable loss and deepest sorrow, the American Heart Association records the sudden and untimely death of its Medical Director, Dr. Eugene B. Ferris, on September 26. Dr. Ferris was stricken by a heart attack as he worked at his desk. He was 52 years old.

During a distinguished career of 27 years, Dr. Ferris' outstanding accomplishments in scientific research, medical education and medical practice had won him wide renown. Before taking up his duties at the Association on February 1, Dr. Ferris was Professor of Medicine and Chairman of the Department of Medicine at Emory University School of Medicine, Atlanta, Ga.

Active in Heart Association affairs for many years, he was elected a Vice President of the national Association in 1955, a post he relinquished on his appointment as Medical Director.

He earlier served as Chairman of the Medical Advisory Board of the Association's High Blood Pressure Research Council and as a member of the Executive Committee of the Association's Scientific Council. He had also been prominently associated with the Cincinnati and the Georgia Heart Associations.

From 1946–1952, Dr. Ferris was successively Instructor, Assistant Professor, Associated and full Professor at the University of Cincinnati College of Medicine, Department of Medicine, where he was also active as Director of the Commonwealth Fund Psychosomatic Teaching Project.

During World War II, Dr. Ferris' research interest centered around aviation medicine. He directed a pioneer study of the effects of high altitude on humans, using himself and student volunteers as subjects.

His clinical activities in Atlanta included service as Chief, Medical Service, Grady Memorial and Emory University Hospitals and as consultant and member, Dean's Committee, Atlanta Veterans Hospital. While in Cincinnati, Dr. Ferris was a member of the Directing Staff, Cincinnati General and Holmes Hospitals, and also of the Visiting Staff, Bethesda Hospital.

Dr. Ferris was born in McNeill, Mississippi on June 24th, 1905. He was a graduate of the Mississippi State College and received his medical degree at the University of Virginia.

Formerly editor of the Cincinnati Journal of Medicine, Dr. Ferris became editor-in-chief of the American Journal of Clinical Investigation in 1948. Dr. Ferris was a former President of the American Society for Clinical Investigation and former President of the American Psychosomatic Society. He was a member of the Board of Regents of the American College of Physicians and a member of the Association of American Physicians and the American Clinical and Climatological Society.

Dr. Ferris was a member of the Cardiovascular Study Section, United States Public Health Service, and served as Consultant to the Surgeon General, United States Army, from 1949–53. He was actively engaged in basic and clinical medical research throughout his career and published many scientific papers concerned particularly with the heart and blood vessels, heat regulation of the body, aviation medicine and physiology, and pulmonary physiology.

ABSTRACTS OF PAPERS

of the

30th SCIENTIFIC SESSIONS

of the AMERICAN HEART ASSOCIATION

October 25–28, 1957

Hotel Sherman

Chicago, Ill.

The Program of these Sessions was published in the October issue of Circulation.

ABSTRACTS OF PAPERS

LEWIS A. CONNER MEMORIAL LECTURE

Rheumatic Heart Disease: A Challenge

Charles H. Rammelkamp, Jr., Cleveland, Ohio

Rheumatic fever and rheumatic heart disease continue to cause considerable disability in children and young adults. Today, the medical profession is presented with the opportunity to reduce significantly the total number of cases occurring each year in the general population and to alter in a favorable fashion the evolution of valvular heart disease in patients who have already experienced rheumatic fever.

It is not generally appreciated that there are at least 4 possible methods by which the physician may alter the incidence of rheumatic heart disease. These methods are based on accumulated data obtained by numerous investigators during the past two decades. The appreciation of the role of the group A streptococcus in the production of rheumatic fever is primarily responsible for the development of effective preventive and even therapeutic measures. The application of this knowledge to the control of rheumatic heart disease has been assisted by contributions from the fields of public health, epidemiology, and clinical medicine. It is now apparent that even further advances can be expected. By stimulating additional research, the pathogenesis of rheumatic heart disease may finally be solved.

GEORGE E. BROWN MEMORIAL LECTURE

Current Evaluation of the Thrombosis Problem

Nelson W. Barker, Rochester, Minn.

Intravascular thrombosis is still the cause of a large percentage of the deaths attributable to cardiovascular disease, although in many instances it may be considered a complication of an antecedent pathologic process in the blood vessels. Even when it is not lethal, intravascular thrombosis may be the cause of much disability.

In spite of much research and study, our knowledge concerning the pathogenesis of intravascular thrombosis has not increased much during the past 50 years. One or more of the 3 factors: endothelial disease or injury, relative stasis of blood flow, and increased coagulability of the blood, are still held to be responsible for intravascular thrombosis. During the past 15 years, research has increased somewhat our knowledge concerning disturbances in blood flow and changes in the various factors which may accelerate coagulation of the blood. In many patients who have had thrombosis, certain tests may show acceleration of the clotting process. When patients who have had thrombosis are compared with normal persons, none of these tests has shown consistent distinguishing differences and many of the tests have been difficult, time-consuming and subject to technical error.

Well-directed anticoagulant therapy has been partially successful in the attack on the thrombosis problem, and this therapeutic approach has been gradually extended during the last 15 years. There are still differences of opinion regarding the choice of available anticoagulants, methods of testing for their effect, and exact indications for their use. It is probable that some thrombosis has been prevented by measures designed to improve blood flow, and concerted attack is being directed toward at least some of the diseases which produce alterations in the endothelium of the blood vessels. Recent advances in vascular surgery have resulted in the successful removal or bypassing of thrombotic obstruction of blood vessels in a small percentage of cases. The use of fibrinolytic agents in an attempt to disintegrate freshly formed thrombi is still in the experimental stage.

There is need for continued well-directed research in our attack on the thrombosis problem. This should include further investigation of the pathogenesis, the exploration of tests for the early detection of defects in coagulation which may augment the tendency to thrombosis, more efficient and better-controlled anticoagulant therapy, improved surgical technics for removing thrombotic obstructions, and further exploration of the possibility of medicinal thrombolysis.

SELECTION OF PAPERS: Abstracts of papers and exhibits submitted were evaluated by the Program Committee of the appropriate council and the Subcommittee on Exhibits of the American Heart Association. The final selections were made by the over-all Program Committee of the American Heart Association on the recommendations of the Council Program Committees. No senior author was included on the program more than once, nor were papers accepted if the author had submitted a proposal for a scientific exhibit on the same topic.

Abstracts are printed alphabetically according to the senior authors.

(*) *Research Fellow, American Heart Association, 1956–1957.*
(†) *Established Investigator, American Heart Association, 1956–1957.*

Effects of Acetylcholine, Adrenalin, Noradrenalin, and Oxygen on the Pulmonary Hypertension of Normal Newborn Infants

Forest H. Adams, Los Angeles, Calif., John Lind, Stockholm, Sweden, and Lauri Rauramo, Turku, Finland.

In a previous report, the present authors demonstrated that normal newborn infants regularly have right ventricular and pulmonary hypertension of a moderate degree, and a significantly large left-to-right shunt of blood through the ductus arteriosus persisting up through the third day of life. A number of physiologic studies have been performed in patients with pulmonary hypertension due to disease, but none have been performed in this situation where it exists normally.

Six normal infants and 1 lamb, all under 24 hours of age, were the subject of this investigation. A right heart catheterization was performed under rectal basal anesthesia, using the saphenous vein. Base line observations were made, following which varying doses of acetylcholine, adrenalin and noradrenalin were injected into the heart through the catheter, and the pressure and heart rate was recorded.

Under these circumstances acetylcholine produced little or no change in the heart rate, but frequently produced a slight increase in the pulmonary hypertension, which persisted for several minutes. Noradrenalin and adrenalin both produced a tachycardia and a marked increase in the pulmonary hypertension. One hundred per cent oxygen had no effect on the pressure or the heart rate when administered by mask for 5 minutes. The observations on the lamb were similar, differing only in minor respects.

Physiologic Changes in Ventricular Septal Defect Following Intracardiac Surgery

Paul Adams, Ray C. Anderson, Peter Allen, and C. Walton Lillehei, Minneapolis, Minn.

Thirty-five patients who have survived closure of their ventricular septal defect have been restudied approximately 1 year following surgery.

Twenty-seven patients on recatheterization showed no residual left-to-right shunt, and in all but 3 cases there was a significant drop in pulmonary artery pressure consistent with the decrease in pulmonary flow. In 3 patients there was no drop in pulmonary artery pressure, and calculated total pulmonary resistance increased. In 2 of these patients, lung biopsy material was present and exhibited intimal proliferation of small pulmonary arterioles. There were 8 patients with demonstrable residual left-to-right shunts, 5 of whom had significant reduction in pulmonary artery pressure and were noticeably improved. Three of these patients were unimproved.

Growth failure preoperatively was common and nearly all patients returned to average growth levels postoperatively when the shunt had been closed and pulmonary hypertension was not a prominent preoperative feature.

Increased pulmonary vascularity estimated by roentgenogram soon returned to normal when the shunt was closed, but cardiomegaly disappeared less strikingly.

All patients had incomplete or complete right bundle-branch block. The percentage fall in pulmonary artery pressures from the preoperative high levels showed no correlation with the presence or absence of left ventricular diastolic overloading on the electrocardiogram preoperatively.

Physiologic Changes with Age in Ventricular Septal Defect

Paul Adams, Ray C. Anderson, Peter Allen, and C. Walton Lillehei, Minneapolis, Minn.

The "natural history" of ventricular septal defect has recently become of greater interest since it is now possible to correct these malformations by intracardiac surgery. This report deals with 30 patients having ventricular septal defect who have had 2 successive catheterizations at intervals varying from 1 to 8 years apart prior to intracardiac surgery. There were 5 patients who showed a distinct fall in their measured pulmonary artery pressures over the span of years between catheterizations. The physiologic measurements of these patients taken as a group show a fall over the average of 2 years in total pulmonary resistance from approximately 2.5 times normal to 1.5 times normal. The pulmonary flow per square meter of surface area fell during the same interval. The second group consists of 12 patients who showed very slight changes in their mean pulmonary artery pressure or other physiologic variables over an average length of time of 4 years between studies.

Thirteen patients, however, showed definite signs of increasing pulmonary artery pressures over the years and confirmed the clinical impression that in many instances this is a severely progressive malformation. Three of these patients had essentially normal mean pulmonary artery pressures when first studied indicating a "latent" period at least up to 9 years of age in 2 of the cases. The remainder of the patients, however, had noticeably elevated pressures when first seen, and these progressively increased over the years between the studies. Lung biopsy or autopsy tissue was available from 6 of these patients

5 of whom have shown intimal proliferation of the small pulmonary arterioles of severe degree. Total pulmonary vascular resistance compared to normal values represented an increase from twice normal to over 3 times normal. The increase in pressure did not appear to be due solely to the increase in pulmonary vascular resistance but due equally to increased pulmonary flow from approximately 2 to 3 times systemic flow over the interval.

It may be reasonably hypothesized that a small number of patients have no "latent" period and begin their progressive course from near birth, others with varying intervals of "latency" from 1 to 15 years. The patients showing no change during the period studied may begin subsequently to take a progressive course.

Pulmonary Diffusing Capacity in Valvular and Congenital Heart Disease

J. Howland Auchincloss, Jr., Robert Gilbert, and Robert H. Eich, Syracuse, N. Y.

While intracardiac septal defects and valvular lesions of the left heart both tend to increase the volume of blood in the major pulmonary blood vessels, it might be expected that they would have opposite effects on the diffusing characteristics of the lung. An estimate of these characteristics was obtained, using the single breath carbon monoxide technic; 16 patients with congenital defects of the cardiac septum were studied and were compared with 13 patients suffering from mitral and aortic valvular heart disease. The normal range of the diffusion characteristics found by this technic was also determined by the study of 19 normal subjects.

The inclusion of patients in both groups who were in greatly different phases of the disease process, has lead to an appraisal of results according to several criteria: (a) clinical severity, (b) reduction of vital capacity, (c) pulmonary artery pressure, and (d) pulmonary blood flow. By all of these criteria, except that of blood flow, the patients with septal defects tended to have larger diffusing capacities than those with valvular heart disease. When both groups were combined, it was possible to relate the diffusing capacity to pulmonary blood flow; this relationship was reasonably well defined over the range of reduced, normal and moderately elevated levels of pulmonary blood flow. Ten of the 16 patients in the septal group had elevated diffusing capacities; 1 patient with marked pulmonary hypertension and shunt reversal at exercise had a reduced value.

The study serves to emphasize the importance of pulmonary blood flow in determining the efficacy of pulmonary gas diffusion, and suggests that diffusing capacity measurements may be of value in assessing damage to the pulmonary circulation caused by congenital or acquired heart disease.

Neostrophegenic Mobilization of the Stenotic Mitral Valve (Rehinging of the Septal Leaflet)

Charles P. Bailey, Houck E. Bolton, and Henry T. Nichols, Philadelphia, Pa.

Because of the technical limitations and inadequacy of the usual mitral commissurotomy procedures, the likelihood of producing mitral insufficiency, and the frequency of recurrent mitral stenosis, the authors are recording an entirely different type of operative technic for mitral stenosis. Essentially this consists of the utilization of the technical advances of the right-sided approach, through which it is possible to convert the irreparably damaged flutter valve mechanism of the stenotic mitral valve into a highly efficient functional flap valve. In over two thirds of operated patients, it is estimated that 90 per cent, or more, of normal valve function can be re-established.

It is believed that this procedure represents a distinct advance over the modern type of commissurotomy. With this operation, now performed in over 300 patients, it is possible to correct the auscultatory and dynamic abnormalities of mitral stenosis. If this can be accepted as an indication, the neostrophegenic mobilization may be capable of eliminating the paradox of subjective response to commissurotomy without objective confirmation.

Use of the Heart-Lung Pump for the Direct Surgical Repair of Atrioseptal Defects

Alvin A. Bakst, Philip Crastnopol, and Irving G. Kroop, Brooklyn, N. Y.

Defects of the atrial septum may be divided into 3 categories, those of the foramen secundum, those of the high septum secundum which are usually associated with transposition of the right pulmonary veins, and those of the septum primum.

Obviously the accurate evaluation and repair of these defects must be under direct vision. In this fashion all defects of the septum secundum can be directly repaired. Defects of the septum primum require the careful placement of an Ivalon prosthesis.

Eight patients have been operated upon for the open repair of the defect, using total cardiopulmonary bypass in the beating heart. In all, the defects have been completely repaired, with correction of transposed veins when necessary. In 3 patients multiple defects, not recognized during closed digital exploratory atriotomy, were visualized and corrected. In 1 patient the superior vena cava was transposed into the left atrium, associated with transposition of the middle and upper lobe pulmonary veins. The technic of the successful total correction of this lesion will be described. In 1 patient a prior attempt at closure of a huge defect was made under hypothermia without success. This defect was easily repaired by use of the heart pump.

It would seem that the heart-lung pump provide

a means of safely repairing atrioseptal defects under direct vision, using an unhurried, accurate and meticulous technic.

Changing Clinical Picture of Tuberculous Pericarditis

Samuel Bellet and Sally J. Holm, Philadelphia, Pa.

A comparison is made between a series of 78 cases of tuberculous pericarditis, observed at the Philadelphia General Hospital between 1930 and 1937 before the antibiotic era (series A), and a series of 29 cases studied from 1950 to 1956 during which period other methods of therapy, including antibiotics and surgery were available (series B). Necropsies were available in 61 cases (78 per cent) of group A, and in 12 cases (41 per cent) of group B.

In series A, the incidence was 0.7 per cent of all necropsies, 70 per cent were Negro, the clinically primary type was observed in 33 per cent, and in the remainder it was secondary to tuberculosis of the lungs or a tuberculous focus elsewhere in the body. In series B, the incidence was 0.38 per cent, 98 per cent were Negro, the clinically primary type was observed in 27 per cent, and in the remainder it was secondary to a tuberculous focus elsewhere in the body.

The modes of onset were as follows: (1) with manifestations of an upper respiratory infection, (2) initial symptoms suggestive of "rheumatism," (3) gastrointestinal disorder, (4) when symptoms of active pulmonary tuberculosis were present, the symptoms of pericarditis were often obscured by the underlying pulmonary process, (5) the onset was inconspicuous and the initial examination disclosed adherent pericardium, which sometimes develops early in the course of this disease.

After a diagnosis of pericardial disease was made, a tuberculous etiology was suspected from the following findings: (1) the presence of tuberculosis in the lungs or elsewhere, (2) a positive PPD test, (3) the presence of a large pericardial effusion, which was usually serofibrinous; with a removal of fluid and injection of air, the effusion was found to be large, the heart small, and the parietal pericardium thickened, (4) the electrocardiogram usually showed inverted T waves in both limb and precordial leads; RST segment elevation, even in the acute stage, was uncommon, (5) in the clinically primary type, the differential diagnosis involved the rheumatic and nonspecific types of pericarditis. The final diagnosis was established by the recovery of the organism from the pericardial fluid and by histologic examination at surgery and necropsy.

Prognostically, a comparison of these 2 series is informative in that only 11 of 78 cases (14 per cent) went into an arrested or healed state in group A, whereas in group B, 11 of 25 cases (40 per cent) followed were still living 1 to 5 years after treatment.

Newer Technics for Left Heart Catheterization

Bernard A. Bercu and Gerald A. Diettert, St. Louis, Mo.

Left heart catheterization has become a routine procedure in many hospitals. Although its value cannot be questioned, deficiencies need to be corrected in order to improve interpretation. The authors have added the use of dye dilution curves and direct left ventricular puncture to the routine left heart catheterization method.

Approximately 125 patients have been catheterized by the transthoracic method of left atrial puncture. In only 65 per cent of these patients was it possible to pass a catheter through the needle into the ventricle. In 8 patients the ventricle was deliberately punctured directly, using the same approach by either pointing the needle slightly caudad as it was advanced or by entering the chest 1 interspace below the site used for left atrial catheterization. This method has proved satisfactory, but the left ventricle was not uniformly entered. In 10 patients direct left ventricular puncture via the anterior percutaneous route was used, entering the chest 1 cm. below and lateral to the apex impulse. No difficulty has been encountered and the ventricular cavity was easily entered on each occasion. Left ventricular pressures were compared with simultaneous arterial pressure tracings, and significant gradients between the 2 systolic pressures correlated closely with aortic stenosis found at subsequent operations.

Dye dilution curves have been recorded following the injection of Evans blue dye into the left atrium in patients with mitral valve disease. In 5 patients it has been possible to determine the presence of significant mitral insufficiency by a decrease in the rate of decline of the dye concentration curve. In a similar manner, by injecting the dye into the left atrium or left ventricle, dye dilution curves have provided evidence for the degree of aortic insufficiency if significant mitral insufficiency was not present. The results have been corroborated in a series of 6 patients.

Modified Cardiopneumonopexy for Coronary Artery Disease

Bernard A. Bercu and Gerald A. Diettert, St. Louis, Mo.

A number of surgical procedures have been described for the relief of coronary artery disease. Experimental studies have indicated that the chief effect of these operations has been the stimulation of intercoronary collaterals.

It has been established that ligation of a branch of the pulmonary artery results in an extensive bronchial artery collateral system without producing untoward effects. It was felt such a collateral network containing fully oxygenated blood at systemic pressures could be utilized for revascularization of the myocardium.

The procedure employed on a series of mongrel dogs resembles that described by Liebow. The branches of the left pulmonary artery supplying the left upper lobe and lingula were isolated and cut. The pericardium was opened and the anterolateral surface of the left ventricle cauterized with 88 per cent phenol to destroy the epicardium. Similarly, the mediastinal surface of the lingula was cauterized with phenol. The lingula was then tacked to the left ventricular surface with 4-0 arterial silk. In the series, there were no deaths attributable to the operation. Suitable controls without cauterization and/or pulmonary artery ligation were also prepared. In a few animals, chronic coronary artery occlusion was induced by placing Ameroid, a hydroscopic plastic, around branches of the coronary arteries.

After a period of 2 to 9 months, the animals were reoperated upon and coronary artery flow rates determined. The animals were then sacrificed and permanent casts of the bronchial, coronary, and pulmonary artery systems obtained for anatomic study. An extensive bronchial-coronary artery collateral system could be demonstrated. Flow studies revealed that a significant amount of blood (10–15 per cent of coronary flow) was supplied to the coronary arteries via the bronchial collaterals.

This operation has been performed on 4 patients with severe angina pectoris who have been followed for 2 to 8 months with promising results.

Dyspepsia of Effort, and Delayed Dyspepsia of Effort, in Patients with Coronary Artery Disease

Bernard H. Berman, Washington, Pa.

In taking routine histories, the symptoms of angina of effort and those of dyspepsia are elicited, but the association of the two is often neglected. Dyspepsia associated with effort, or dyspepsia following effort, may be overlooked in patients with coronary artery disease.

Seventy patients with proven coronary artery disease were closely observed for the occurrence of dyspepsia of effort, and delayed dyspepsia of effort. The relative frequency of belching, bloating, abdominal pain, nausea, and sialorrhea were specifically noted as they applied to effort and the period following effort. Patients noting effort dyspepsia were given an upper gastrointestinal series, gallbladder and glucose tolerance tests.

Eight patients gave histories of dyspepsia with effort, or dyspepsia delayed a few minutes or even an hour following effort. In 3 cases, dyspepsia overshadowed the angina of effort.

In this series, dyspepsia of effort bore no relation to the severity of the coronary or myocardial disease. One patient with an active duodenal ulcer had no dyspepsia of effort. No definite relation between the occurrence of dyspepsia of effort and the site of the myocardial infarctions was noted. Two cases of cardiac aneurysm had no indigestion. There was no definite correlation between the emotional makeup of the individual and the presence of dyspepsia of effort. A most severe neurotic, with a history of marked angina for 10 years, had no dyspepsia of effort.

The finding of delayed dyspepsia of effort, occurring from a few minutes to as late as an hour following exertion, may be an important clue to the diagnosis of coronary artery disease. This information is usually not volunteered by the patient and often is not secured on the first interview.

The use of the terms "dyspepsia of effort" and "delayed dyspepsia of effort" is justified in selected cases of coronary artery disease, and in these cases may be equally as valid as the term "angina of effort."

Electrocardiographic Findings in Cardiac Amyloidosis

Michael Bernreiter, Kansas City, Mo.

Six cases of cardiac amyloidosis will be reported. The outstanding clinical finding was intractable heart failure. The electrocardiogram, while not specific, gave a suggestive pattern in all cases, and was quite helpful in leading to the final correct diagnosis. The pattern consists of low QRS voltage in the extremity leads, and complete or almost complete inversion of the QRS complexes in the first 3 or 4 precordial leads. Rhythmic disturbances were frequently observed and, in 1 case, electric alternation of the P waves. The final diagnosis was established by liver biopsy, skin biopsy, or autopsy findings.

Treatment of Shock with Mephenteramine in High Dosage

Arthur Bernstein, Bernard Robins, Fred B. Cohen, and Franklin Simon, Newark, N. J.

Difficulties with the use of l-norepinephrine as a pressor substance in the treatment of shock due to conditions other than blood loss consist of the need of very exact titration, the not infrequent development of tissue slough at the site of accidental infiltration, and the occasional production of cardiac arrhythmias.

Recent work demonstrating the antiarrhythmic and positive inotropic effect of mephenteramine (N-methyphenyl tertiary butyl amine sulfate) has stimulated our re-examination of this substance as a pressor agent in clinical shock and hypotension, particularly when due to cardiovascular disease. Our previous experience with this agent was unsatisfactory, using the dosages originally recommended. Based on wide experience with larger doses, chiefly by anesthesiologists, we have established a new schedule of administration which has clinical effectiveness.

Mephenteramine was administered to 25 patients with vascular collapse, chiefly due to cardiovascular disease, by giving 30 to 60 mg. intravenously, fol-

lowed by an intravenous drip of 540 mg. in 500 ml. of glucose solution. A significant blood pressure response with reversal of clinical shock was obtained in 16 cases (64 per cent). No adverse arrhythmias or severe side effects occurred in this series.

Factors Influencing the Hypocholesterolemic Effect of Sitosterol

Maurice M. Best and Charles H. Duncan, Louisville, Ky.

Varying concentrations of free and esterified β-sitosterol have been added to the diet of 1 per cent cholesterol-fed rats. The resulting levels of serum and liver cholesterol at the end of 2 weeks have furnished information relative to the previously reported hypocholesterolemic effect of sitosterol in man. Free sitosterol, added in the following percentages: 0, .5, 1, 2 and 5, resulted in mean liver cholesterol levels of 1404, 825, 467, 303 and 255 mg./100 Gm. liver respectively (normal 270). Reduction of liver cholesterol to this degree is observed only when the cholesterol and sitosterol are ingested at the same time, as in these studies. When fed to the rat on separate pellets, the mean liver cholesterol of a group receiving 1 per cent cholesterol and 5 per cent sitosterol was 838 mg./100 Gm.

That β-sitosterol interferes with cholesterol absorption only when it is present in the gut as the free alcohol is suggested by the results of the administration of a series of sitosteryl esters. Each was added to the 1 per cent cholesterol diet in an amount equimolar to 5 per cent free sitosterol. The relatively stable sitosteryl palmitate exerted very little effect on liver cholesterol, the mean concentration being 862 mg./100 Gm. The more soluble and more readily hydrolized formate and acetate retain most of the effect of the free sterol, mean liver cholesterol values being 359 and 300 mg./100 Gm., respectively. Sitosteryl proprionate was less effective, the mean liver cholesterol being 531 mg./100 Gm. Serum cholesterol differences paralleled in general the differences in liver cholesterol, though their magnitude was less.

These observations suggest that the hypocholesterolemic effect of sitosterol in man may be significantly influenced by dosage, relationship of administration to time of food ingestion, and to the chemical state of the sitosterol.

Probable Critical Cooling Level During Immersion Hypothermia

Emil Blair and Russell L. Zimmer, Denver, Colo.

Recent clinical and experimental evidence suggest that relatively deep levels of hypothermia (25 to 27 C.) result in undesirable circulatory changes, including arrhythmias and baroceptor disturbance. It is recommended that the depth of hypothermia be kept in the range of 29 to 30 C. for intracardiac surgery. The present study is an attempted experimental evaluation of the effect of various levels of hypothermia on the circulation, with particular view on the reflex mechanisms. The medium of total inflow circulatory occlusion and release was used. This permits a study of certain baroceptor activity, as well as autonomic response.

Dogs under Nembutal anesthesia with artificial ventilation were used. The animals were divided into the following groups: A, control normothermia; B, "moderate" hypothermia (35 to 29 C.); C, "deep" hypothermia (28 to 25 C.). The occlusion was maintained for 3 minutes in all groups.

Release of the occlusion—blood pressure: Group A, "overshoot" with reflex bradycardia appeared within 30 to 45 seconds, the latter abolished by vagectomy or carotid denervation. Group B, phenomena same as in group A, in 3 of every 4 dogs Group C, no "overshoot" was observed. Heart rate slowed in one third of the dogs, with no change following vagectomy. Central and peripheral venous pressures, which were elevated during occlusion, promptly fell to normal levels on release at all hypothermic levels.

The "overshoot" following release of total circulatory occlusion is the result of increased stroke volume (increased venous return to the heart and myocardial work) and increased flow into a constricted vascular bed. The bradycardia is a reflex response to the hypertension and is present during hypothermia, except at deep levels. Within the limits of this study, experimental evidence confirms a probable "critical" level of hypothermia (28 to 29 C.) below which there may occur disturbances of the circulation, including the cardiovascular baroceptors.

Simultaneous Observation of Reflex Constriction in Isolated Saphenous and Forearm Venous Segments

Stuart Bondurant and Sidney D. Leverett, Wright-Patterson AFB, Ohio.

To investigate reflex changes in the tone of the saphenous vein and of superficial forearm veins, tributary-free segments have been hemodynamically isolated between 2 occlusive pneumatic tourniquets (380 mm. Hg). Venous catheterization from a puncture site distal to the tourniquets allowed the catheter tip to lie within the intact segment. Reflex constriction of the isolated segment caused an increase in pressure, which was measured through the catheter. To establish the fact that the segments were leakproof and free of tributaries, pressure was followed after the segment was emptied, and after it was overfilled through the catheter.

The following data are based on 85 observations of pressure change in forearm venous segments (FVS) of 8 subjects with 41 simultaneous observations of pressure change in saphenous venous segments (SVS) of 4 subjects. With the subject at rest, pressure in the segment was relatively stable, changing by 2 ± 3 mm. Hg during control periods.

Following a standard Valsalva maneuver, FVS pressure increased above the resting level by a mean of 10 ± 5 mm. Hg, while SVS pressure increased by 13 ± 6 mm. Hg. Following immersion of a contralateral extremity in ice water, FVS pressure increased by 9 ± 8, while SVS pressure increased by 15 ± 6. Following vertical tilt (exposure of the subject to +1 g) FVS pressure increased by 8 ± 9, while SVS pressure increased by 15 ± 17 mm. Hg. Following acceleration on the USAF human centrifuge (exposure of the subject to +3 g), FVS pressure increased by 13 ± 4, while SVS pressure increased by 17 ± 10 mm. Hg.

In every instance, segment pressure increased during each experiment. The large standard deviations reflect the wide range of venoconstrictor activity observed.

Reflex constriction of saphenous venous segments is qualitatively comparable to that observed and previously described in forearm venous segments. Such reflex constriction of leg veins may be of importance during orthostasis and other types of circulatory stress.

Differentiation of Types of Idiopathic Hypercholesteremia by Serum Lipoprotein Distribution and Response to Therapy

Edwin Boyle, Jr.† and Henry M. McLaughlin, Charleston, S. C.

During the treatment of patients with hypercholesteremia of unknown etiology, some with xanthomatosis, it became apparent that their response to different types of therapy (heparin, oral estrogens, lipotrophic agents, and dietary restriction) was unpredictable as judged by the changes in the serum cholesterol. Ultracentrifugal analysis of their serum lipoproteins revealed patterns of distribution that permitted classification of the patients into 4 general groups: (1) β_1-hyperlipoproteinemia (tendinous hypercholesteremic xanthomatosis), (2) β_2-hyperlipoproteinemia (tuberous hypercholesteremic xanthomatosis), (3) mixed β-hyperlipoproteinemia (mixed xanthomatosis and hypercholesteremia), and (4) hyperchylomicronemia (essential hyperlipemia). Response to therapy showed better correlation when the patients were studied as groups.

Conclusions are based on data accumulated over a period of 5 years. The serum lipoproteins were analyzed by the technics described by Gofman and associates, and/or Green, Lewis and Page. The data were compared with the results of a system of analysis combining preparative ultracentrifugation with lipid chemical analysis of several density classes of lipoproteins.

Results indicate that the type and/or distribution of the xanthomata will permit accurate prediction of the lipoprotein distribution in many patients. However, most of the hypercholesteremic patients without xanthomata, "form fruste" type, have a lipoprotein distribution compatible with 1 of the 4 groups mentioned. Conversely, many patients with xanthelasma and slight to moderate hypercholesteremia have a lipoprotein pattern which does not consistently fall into any of the groups characterized above.

Evaluation of any regimen of therapy requires a population which is uniform with regard to the factor under study. Our results indicate that human beings with idiopathic hypercholesteremia are not a uniform population. Indeed, these studies suggest that such individuals represent *several* lipid metabolic diseases with certain marked similarities. Poor correlation of response to therapy when studying samples of such a mixed population substantiate these conclusions.

Method for Detection and Estimation of Magnitude of Aortic Regurgitant Flow

Eugene Braunwald and Andrew G. Morrow, Bethesda, Md.

The magnitude of reverse flow in the aortic arch is minimal in the absence of aortic regurgitation. In the presence of aortic regurgitation, however, reverse flow in the aortic arch is increased. The volume of such reverse flow in excess of that which is normally present represents regurgitant flow across the aortic valve. Aortic regurgitant flow was detected by the injection of indicator dye (indigo-carmine) at various levels in the descending aorta through a catheter introduced percutaneously from the femoral artery. The lowest point in the descending aorta from which injected dye regurgitated back to the ascending aorta and perfused the right ear was determined by means of an oximeter placed on the right ear. The position of the catheter tip was then recorded roentgenographically. In all 7 patients without aortic regurgitation who were studied, dye injected distal to the aortic arch could not be detected in the right ear. In all 10 patients with clinical and hemodynamic evidence of aortic regurgitation, dye injected into the descending aorta regurgitated to the ascending aorta. In 2 of these patients who had clinical evidence of severe aortic insufficiency, dye injected into the aorta below the diaphragm could be detected in the right ear. This technic was found particularly useful in demonstrating aortic insufficiency in 5 other patients with diastolic murmurs at the base of the heart, but without other hemodynamic evidence of aortic valve disease.

Employing aortic pressure-volume relationships obtained from human cadavers, the magnitude of aortic regurgitant flow was estimated. In 15 patients with aortic insufficiency, the estimated regurgitant flow ranged from 0.8 to 2.8 L. per minute per $M.^2$ B.S.A.

Direct Experimental Approaches to the Problem of Intraventricular Diastolic Suction

Gerhard A. Brecher and Abbott T. Kissen, Columbus, Ohio.

Method 1. In open chest dogs, ventricular diastolic inflow from a reservoir situated below the level of the

h art was phasically recorded with a bristle flow m ter. Simultaneously, subatmospheric (negative tr nsmural) intraventricular diastolic pressures were r corded. The atmospheric zero reference level was e tablished by submerging the heart in the saline-fi ed chest. One may conclude that, contrary to prev iling concepts, the intact mammalian ventricle is c pable of drawing blood into its cavity. However, s ch ventricular *vis a fronte* could be demonstrated o ly in nearly empty ventricles. Therefore, pressure-v lume relationships of ventricles were studied. *Method 2.* Negative intraventricular transmural p essures were recorded in empty, quiescent but viable dog ventricles. The ventricular pressure-volume curves were S-shaped, having 1 limb in the negative and another in the positive pressure range. It was concluded that static elastic forces of the ventricular walls account in part for negative ventricular diastolic pressures and that elastic deformation of the walls tends to restore diastolic dimensions to the ventricular cavities. Despite these experiments and those reported by others, the question remained unresolved whether a more nearly normal ventricle, with a residual volume as established by ejection against normal aortic pressures, draws in blood during diastole. *Method 3.* In open chest dogs, the heart was submerged by filling the chest with donor blood. The left atrial wall was extirpated, thereby establishing zero ventricular filling pressure. The entire circulation and arterial pressures were maintained at normal levels by pumping pulmonary venous blood from the chest into the femoral artery. Small systolic aortic pressure pulses were recorded indicating the existence of ventricular ejection and thereby of diastolic suction. This was enhanced by epinephrine. It was concluded that the intact mammalian ventricle working against normal aortic pressures draws a small amount of blood into its cavity with zero ventricular filling pressure.

Ventricular Gradient in Space as Determined from the Twelve-Lead Electrocardiogram

Louis Brinberg, New York, N. Y.

The null-point is pictured at the center of a sphere. On this sphere longitude is measured from the left and ranges from 0° to 180°. The anterior hemisphere is positive; the posterior, negative. Latitude ranges from 0° to 90°. The lower hemisphere is positive; the upper, negative. The spherical coordinates, longitude, latitude, and magnitude, of the ventricular gradient are determined from its frontal and horizontal projections by a simple geometric procedure. Its axis in space is then represented by a point on the surface of the sphere at the determined longitude and latitude, and its magnitude shown by enlarging the point to a round spot the area of which is proportionate to the magnitude. The frontal projection is obtained in the usual manner from the bipolar limb leads. The precordial leads are then examined to determine that axis on which the algebraic area of the ventricular complex is equal to zero. This is the transitional axis, and the axis of the horizontal projection of the gradient is perpendicular to it. The terminus of the horizontal projection is obtained by giving it an X value equal to that of the frontal projection.

The gradients of 49 normal subjects were determined. The mean gradient is at longitude 23°; latitude 38°, and its magnitude is 54.0 μv. seconds. The mean QRS is at longitude −18°; latitude 46°; its magnitude is 22.0 μv. seconds. The angle between these 2 mean vectors was determined by measuring the arc distance between the points by which they are represented with a pair of dividers. It equals 32°, and the bearing of the gradient from QRS is NW 88°. The average deviation from the mean gradient axis for the 49 subjects is 20° and ranges from 3° to 47°.

Modern Study of the Bipolar Esophageal Electrocardiogram in Cardiac Arrhythmias

Daniel A. Brody and John M. Barron, Memphis, Tenn.

The role of bipolar esophageal electrocardiography in the diagnosis of cardiac arrhythmias, especially atrial and nodal, was studied by means of an easily constructed and reliably functioning bipolar esophageal electrode. The midpolar point of the electrode assembly was routinely passed 46 cm. beyond the external nares, and then withdrawn in 1 cm. steps. At each step of withdrawal, simultaneous 4-channel registration was made of each esophageal electrode as a unipolar lead, both esophageal electrodes as a bipolar lead, and a conventional body-surface lead.

Bipolar esophageal leads proved diagnostically superior to unipolar leads, especially upon exploration of a sharply localized transition zone in the upper esophagus. Normal atrial complexes recorded slightly distal to the transition point are large and predominantly positive. When recorded from above the transition point, the complexes are also large, but predominantly negative. The ventricular complexes are comparatively small for both positions of registration. The sharp localization of transition depends primarily upon phase differences, since it is usually possible to pass through transition with surprisingly little change in the form and amplitude of the unipolar atrial complexes.

Due to the critical nature of the transition zone, bipolar electrocardiograms recorded from it are exceptionally sensitive to ectopic atrial impulses, which can almost invariably be recognized as such on the tracings. A further helpful feature is the relatively low amplitude of the ventricular complexes,

which permits easy recognition and interpretation of atrial complexes occurring during the ventricular phase.

In our hands this diagnostic approach has greatly facilitated the recognition of a number of complicated arrhythmias, which probably would have been missed with conventional electrocardiography alone, and which were relatively difficult to diagnose in the unipolar esophageal electrocardiograms. As a result of this study we have evolved a relatively simple and clinically practical system of bipolar esophageal electrocardiography.

Hemodynamics of Coronary Heart Disease: Unified Concept with Practical Therapeutic Applications

Bernard L. Brofman, Cleveland, Ohio.

Recent remarkable technical advances in cardiovascular surgery, particularly the direct surgical approach to coronary obstruction (endarterectomy, anastomotic bypass), call for a critical reappraisal of certain fundamental hemodynamic principles concerned in the pathophysiology of coronary heart disease. This report is based upon coronary blood flow studies in anesthetized dogs and in patients undergoing surgical operation for coronary heart disease, hydraulic model experiments and detailed clinicopathologic examination of a large series of hearts. These are summarized in a series of stylized graphs which demonstrate flow-pressure relationships in the coronary circulation as influenced by such factors as coronary insufficiency, anoxia, increased heart work, various pharmacologic agents, and intercoronary communications. These studies attest to the considerable reactivity of the high-resistance coronary vascular bed in which the sum total of peripheral resistance is determined primarily at the terminal arterial (arteriolar) level; the cross-sectional area of a major coronary artery becomes a determinant of flow only when there is reduction in its lumen beyond a critical level.

The patient with coronary heart disease has a critically compensated, precariously balanced circulation in which relatively "slight" alterations have far-reaching consequences. Tremendous potential for protection of the myocardium is afforded by intercoronary communications, provided they function *in advance* of the occlusive process—collaterals which develop *after* myocardial infarction may actually be deleterious. In a fundamental sense, there is not necessarily a correlation between the *structural* disturbances in the coronary arteries and its *functional* consequences. On the ill-advised assumption that a patient's disability is due to a given structural occlusion in a coronary artery, surgical restoration of blood flow through the chronically obstructed segment may well result in preferential perfusion of a myocardial scar with disastrous consequences for the heart as a whole.

Effects of Induced Hypocalcemia upon the Electrocardiographic Manifestations of Digitalis

Milton J. Brothers and Bernard Kabakow, New York, N. Y.

It is well established that calcium, potassium and digitalis are interrelated in their actions on the myocardium. Essentially, digitalis causes an egress of intracellular potassium, and calcium exerts a stabilizing influence upon the cell membrane, perhaps interfering with the active re-entry of potassium.

Utilizing the chelating action of sodium ethylene diaminetetraacetate (Na-EDTA), 17 patients with a variety of clinical conditions were rendered transiently hypocalcemic by the intravenous infusion, over 4 hours, of 250 ml. of 5 per cent glucose and water containing 4 Gm. of Na-EDTA. In each case the serum calcium was lowered, the average depression being 2.0 mg. per cent.

In 4 patients, with a clinical history and electrocardiographic evidence of digitoxicity as manifested by atrial fibrillation with multifocal premature ventricular contractions, coupling or trigeminy, the manifestations of myocardial hyperexcitability receded or disappeared during the course of the infusion. In 6 additional patients, all on digitalis, with arrhythmias consisting of bigeminy, heart block and supraventricular tachycardia, but whose clinical histories and hospital courses suggested a cause other than digitoxicity for these rhythms, Na-EDTA was ineffectual. In 1 patient, who had never received digitalis, a constant bigeminal rhythm was unaffected by the Na-EDTA.

Another group of 6 patients, all showing marked S-T and T wave depression and T wave inversion, were similarly treated. Four of these, who had been on maintenance digitalis for a long time, showed a significant reversion of these segments toward the isoelectric line. Calcium-EDTA, given as a control to 1 of these patients, had no effect. The depressed segments of the other 2 subjects, who had never been on digitalis, but who had left ventricular hypertrophy and coronary insufficiency, were unchanged by Na-EDTA.

It is suggested that the production of a transient hypocalcemia in certain digitalized patients may be of value in (1) the treatment of digitalis intoxication, (2) differential diagnosis of myocardial hyperexcitability, and (3) in evaluating S-T and T wave changes.

Renal Rheoplethysmogram of the Dog

George E. Burch and John H. Phillips, Jr., New Orleans, La.

For the first time, the renal circulation has been studied rheoplethysmographically, a method in which the time courses of volume, rate, and a-

celeration of inflow, outflow, and difference between inflow and outflow in a part are recorded continuously and simultaneously for a pulse cycle. Applicability of venous occlusive rheoplethysmography to the study of physiologic and pharmacologic renal circulatory phenomena were demonstrated. Several hundred renal rheoplethysmograms of 5 anesthetized normal dogs were obtained under control conditions and during acute increase or decrease in systemic blood pressure induced by norepinephrine and hexamethonium.

The control basal component of renal flow was invariably extremely high, with relatively smaller rates of superimposed complemental pulsatile flow for both the arterial and venous segments of the circulation.

The extremely high basal renal flow was of much greater magnitude per gram of part than basal digital flow in man, indicating proportionately less resistance to renal than to digital flow and reflecting flow primarily through functionally large arteriovenous communications that offer relatively little resistance. Basal flow was so rapid that, at basal rates, a volume of blood equal to the volume of the average-sized kidney studied (weight 22.0 Gm.) would pass through the organ in 31 seconds. If maximal systolic rates were to prevail throughout the pulse cycle, this time would be reduced to 21 seconds. Thus, basal flow is mainly responsible for the high rates of renal flow. The magnitude of the superimposed pulsatile complemental flow produced by the heart beat exceeded that for the human digit slightly, if at all.

Renal rheoplethysmography offers an excellent means of studying circulatory dynamics in many organs. These acute experiments showed that norepinephrine and hexamethonium, as used therapeutically in man, probably cause no significant decrease in renal blood flow.

Correlative Study of Postmortem, Electrocardiographic and Spatial Vectorcardiographic Data in Myocardial Infarction

George E. Burch, Leo Horan, Joseph Ziskind, and James Cronvich, New Orleans, La.

Vectorcardiograms and electrocardiograms recorded before necropsy in 160 subjects were correlated with gross and microscopic postmortem data in 59 infarcted hearts. In addition to general expectations, results yielded the following new discoveries:

Infarction in areas depolarized after the early phase of the electric cycle produced recognizable alterations in the QRS sÊ-loop. Lateral wall infarction shortened vectors in midtemporal portions; posterolateral basal infarcts altered terminal portions recognizably. Associated alterations in ECG were not noted before sVCG observations.

Six of 33 hearts had posterior infarcts unsuspected in sVCG or ECG. Histologic studies suggested sufficient electrically active, spatially oriented network of muscle interspersed among scars to maintain reasonably normal manifest electric activity.

ECG alone disclosed posterior infarction in 12 of 33 cases and was strongly suggestive in 4 others; sVCG alone revealed posterior infarction in 8 of 33 cases and was strongly suggestive in 9 others. High posterior infarction was recognized by late deformity in QRS sÊ-loop in 6 cases and by ECG in 1.

Seven of 26 hearts had anterior infarcts undiscovered in sVCG; 4 of these had multiple scars with interspersed network of apparently normal muscle.

Associated LVH was detected by ECG in 10 of 20 instances and by sVCG slightly more accurately; associated RVH was observed by ECG in 3 of 13 instances and by sVCG in none. Anterior infarction with combined hypertrophy was missed in both tracings in 7 instances.

Ten hearts had ventricular aneurysms, 7 large ones with fairly characteristic ECG and sVCG.

Electric diagnosis of infarction was missed in less than 15 per cent of 59 cases by ECG or sVCG alone and in less than 5 per cent by both.

By presenting the depolarization complex in greater detail, sVCG improved accuracy of diagnosis of infarction. Electrocardiographic diagnosis could be improved by increasing galvanometer sensitivity and recording speed.

Spatial Vectorcardiogram and the Aging of Man

George E. Burch and Lawrence Golden, New Orleans, La.

The spatial vectorcardiogram was recorded, with the use of the equilateral tetrahedral reference system, on 226 normal subjects between the ages of 20 and 72. Wire models of the QRS sÊ-loops were constructed from each record. Configurations and measurements of QRS and TsÊ-loops were compared for the various age groups. The traces were studied for a previously undescribed characteristic, "distortion" of the QRS sÊ-loop, i.e., major irregularities in contour.

A close similarity was noted for all age groups for both the magnitude and spatial orientation of the maximal mean instantaneous vectors of the QRS and TsÊ-loops, except that these loops tended to become more horizontally oriented in the older age group.

Whereas all QRS sÊ-loops could not be arbitrarily classified with respect to presence or absence of distortion, in most instances such a classification was readily made. Progressive, significant increase in major irregularities in the QRS sÊ-loop were observed as age advanced. Distortion occurred in 22.5 per cent of the cases of the 20-year-old group and continued to rise in incidence with each decade, so that 88.8 per cent of the QRS sÊ-loops of the 60-

year-old group were distorted. With aging, the QRS sÊ-loop manifested greater irregularities and less smoothness in contour when the conventionally recorded electrocardiogram was considered to display no abnormalities.

Thus, the more detailed recording of the depolarization process by the sVCG revealed subtle changes with age that probably could be demonstrated equally well electrocardiographically by means of more sensitive galvanometer and high paper speed. Although the distortions noted may reflect extracardiac as well as intracardiac changes with age, the changes in the time-course of depolarization associated with the aging process most probably produced the sVCG alterations, the clinical significance of which remains unknown.

Augmentation of Diastolic Arterial Pressure by Mechanical Means: Effect on Coronary Sinus Flow

Gus G. Casten, William P. Murphy, Jr., and John C. Alley, Miami, Fla.

Protracted hypotension due to myocardial infarction is accompanied by a mortality rate of approximately 80 per cent. Reduction of the force of myocardial contraction due to infarction with resultant lowering of aortic pressure further diminishes coronary flow. Since diastolic aortic pressure is of major importance in effecting coronary flow, it is toward a controlled increase of this pressure that work has been directed. Mechanical methods of intermittent pressure increase have been investigated and found to be effective.

An electronic timing system triggered by the electrocardiograph activates a valve, allowing blood to flow intermittently from a pressure reservoir into a dog's femoral artery. Using a 2 mm. arterial cannula, a pressure of approximately 10 pounds per square inch is required to increase significantly the carotid diastolic pressure. In 6 dogs rendered hypotensive by venesection, total coronary sinus outflow varied between 40 and 70 ml. per minute. Increasing the diastolic pressure every third heart beat by the above method increased the flow 80 to 140 ml. per minute. The average increase was 100 per cent or more. Blood was withdrawn from a venous site at a rate approximately equivalent to infusion so that uniform hypotension was maintained. Systolic pressures were essentially unaltered.

These results have led to the construction of a small extracorporeal blood pressure generator which withdraws blood from the femoral artery into a chamber during systole and forcibly returns it during diastole. This device has produced an increase in coronary sinus outflow similar to that produced by the original method.

Our experience has shown that a selective increase in aortic diastolic pressure can be accomplished by mechanical means. The resultant increase in coronary sinus outflow has been significant. The possible therapeutic implications of the use of this selective blood pressure generator in situations of diminished coronary blood flow are apparent.

Electrolyte and Water Metabolism in Cardiac Patients with Early Congestive Heart Failure

Aram V. Chobanian, Belton A. Burrows, and William Hollander, Boston, Mass.

This study was undertaken to determine whether any alterations in electrolyte and water metabolism occur in heart failure prior to development of peripheral edema. Fifteen patients with symptoms but no striking signs, of heart failure were included in the study. All showed mild to moderate elevation of pulmonary artery pressure with or without reduction in cardiac output or prolongation of circulation time. None had elevation of right ventricular filling pressure above 10 mm. Hg. Although peripheral edema was absent, there were significant increases in exchangeable body sodium and extracellular fluid volume in the cardiac group as compared with 25 control subjects. Exchangeable body potassium was normal or slightly reduced. Although body sodium and extracellular fluid volume were increased, the cardiac patients were able to tolerate 10 Gm. of salt daily without change in signs or symptoms, or retention of sodium. Furthermore, they showed no impairment in sodium excretion when infused with 300 ml. of 5 per cent saline even though renal plasma flow and glomerular filtration rate were significantly reduced. Dietary sodium restriction and mercurial diuretic administration reduced body sodium and extracellular fluid volume, but not to normal levels.

One patient with primary hypoaldosteronism studied during heart failure showed marked elevation of body sodium and extracellular fluid volume despite absence of demonstrable aldosterone production and presence of normal glomerular filtration rate.

In conclusion: (1) in the development of heart failure, a new equilibrium of expanded extracellular fluid volume precedes any demonstrable impairment of renal capacity to excrete sodium, (2) the rises in body sodium and extracellular fluid volume are consistently associated with elevation of pulmonary artery pressure, but may occur without reduction of cardiac output or elevation of right ventricular filling pressure, (3) elevations of body sodium and extracellular fluid volume in heart failure are not necessarily related to increased aldosterone production.

Electrocardiographic Sign of Pulmonary Artery Hypertension in Rheumatic Heart Disease

Francis X. Claps and Alfred J. Kaltman, New York, N. Y.

In the continuing search for a simple clinical means of estimating the pressure in the lesser cir-

cuit caused by mitral stenosis which can help in reaching a conclusion on the advisability of surgical correction, it was noted that a fairly consistent relationship existed between electrocardiographic abnormalities of the ventricular complex in right precordial leads and the right ventricular and the pulmonary artery pressures.

Of an original 47 patients studied by right heart catheterization, there were 12 who demonstrated mean pulmonary artery pressures in excess of 40 mm. Hg with ranges of systolic pressures from 29 to 46 mm. Hg. All but 1 of these demonstrated an R wave in lead V_1 in excess of 0.25 mv., and in all but the 1 exception, the R wave was larger than the S wave. The latter was entirely absent in 6 of the cases. The T wave was usually inverted. Of 10 patients with normal pulmonary artery pressures (mean pressure less than 15 mm. Hg) and in 7 cases with a mean pulmonary artery pressure only slightly elevated (less than 20 mm. Hg) there were none who showed the electrocardiographic abnormality described, although 1 patient did show a vibratory type of QRS in lead V_1.

It is concluded that in rheumatic heart disease with mitral stenosis, an isolated R wave or an R wave taller than the S wave in lead V_1 is a good index of high right intraventricular pressure.

Experimental and Clinical Results with a Practical Membrane Blood Oxygenator

George H. A. Clowes, Jr., and William E. Neville, Cleveland, Ohio.

An artificial blood oxygenator dependent upon diffusion of oxygen and carbon dioxide through thin plastic membranes has been developed and tested. The principles of filming blood between the membranes to obtain the greatest surface area with minimal blood volume and resistance to flow have been worked out. This offers the advantages of a completely closed system.

Animal experiments showed that survival could be obtained after total perfusions of more than 3 hours, indicating absence of emboli or of other untoward effects on the blood by the apparatus.

Four series of experiments were conducted showing that the most important factor in producing survival after prolonged total perfusion is to employ a surface area of membrane adequate to diffuse 100 per cent of the basal metabolic oxygen requirement of each animal into the blood as it passed through the oxygenator. Minimal metabolic acidosis occurred under these conditions with high flow rates. At low flow rates this became greater with increased levels of lactic acid in the blood, but was compensated by a relative respiratory alkalosis. There was moderate cerebral depression following low flow perfusions. When an inadequate oxygenating surface area of membrane was used, severe uncompensated acidosis took place resulting in subsequent death regardless of rate of blood flow.

A series of satisfactory perfusions with this apparatus has been performed in adult patients during cardiac operations. Chemical determinations during the procedures bear out the experimental observations on the absence of severe metabolic acidosis when perfusions are performed with well oxygenated blood at flow rates over 60 ml. per Kg. of body weight per minute. It is the purpose of this paper to describe the apparatus and to present the data which include blood gas and chemical determinations as well as electroencephalographic and electrocardiographic recordings.

Reduction of Reactive Hyperemia Blood Flow in the Foot by Tobacco Smoking and Body Cooling

Jay D. Coffman and J. Edwin Wood, Boston, Mass.

The effect of tobacco smoking and body cooling on the increased blood flow which follows a period of ischemia of the foot was studied. Foot blood flows were measured with a constant temperature (89 F.) water plethysmograph for 8 minutes, following 5 minutes of arterial occlusion on subjects before and again during smoking in either an 83 F. or a 68 F. environment. Total blood flow through 100 ml. of foot during reactive hyperemia (RHBF) was measured.

Smoking decreased RHBF in 15 of 27 experiments in the 83 F. environment. RHBFs averaged 18.0 ml. before and 10.1 ml. during smoking in these 27 experiments. Smoking decreased RHBF in 6 of 14 experiments in the 68 F. environment. Control RHBFs averaged 13.6 ml. before and 9.9 ml. during smoking in these 14 experiments. Cooling the environment decreased RHBF in 14 of 17 experiments. RHBFs averaged 19.9 ml. in the 83 F. environment and averaged 12.6 ml. in the 68 F. environment in these 17 experiments. The range of variability of RHBF without smoking in either environment was 3 ml.

In 12 of 14 experiments on subjects with lumbar sympthectomized limbs, in warm and cool environments, smoking produced no change in RHBF. In 5 of 7 experiments on these same patients, body cooling also did not affect RHBF. Four patients with unilateral lumbar sympathectomies were studied using a plethysmograph on each foot simultaneously. Sympathectomized feet showed no change in RHBF during smoking in 8 warm and cool room experiments, whereas the unsympathectomized feet showed a definite reduction of RHBF during smoking in 6 of the 8 experiments.

These studies demonstrate that tobacco smoking and, more consistently, cooling the environment often reduce postischemia vasodilatation and together may exert additive vasoconstrictor effects. These reductions apparently are mediated via the sympathetic nervous system as shown by experiments on patients with lumbar sympathectomies.

Long-Term Therapy of Hypertension with Cryptenamine and Cryptenamine-Reserpine Combinations

Burton M. Cohen, Elizabeth, N. J.

Cryptenamine, a veratrum viride alkaloid, has been demonstrated experimentally to have a 4:1 ratio as regards hypotensive and emetic properties, suggesting its trial in the clinical treatment of hypertension. Forty-one patients, Smithwick grades III and IV, were treated with cryptenamine or cryptenamine-reserpine combinations for periods up to 2 years.

Initial therapy of all patients was with cryptenamine alone, in doses ranging from 8 to 16 mg. daily, with a decrement of average mean arterial blood pressure from 153 mm. Hg to 121 mm. Hg. Reserpine was added to the therapy of 17 of these patients. The average control mean blood pressure of these latter declined from 158 mm. Hg to 134 mm. Hg on cryptenamine, and fell to 113 mm. Hg on combined therapy. The use of reserpine permitted a decrease in daily cryptenamine rations.

Alleviation of headache and palpitation, decrease in frequency and severity of angina and relief of dyspnea were noted, in descending order of frequency. Cardiomegaly regressed and funduscopic status improved in 60 per cent of the entire group; Electrocardiographic alterations, lessening of proteinuria and azotemia were less regularly observed.

Twenty-eight of 41 patients reported no side effects on cryptenamine alone; emesis occurred in 1 patient. Ten of 17 patients managed with cryptenamine-reserpine mixtures were free of side-reactions.

Oral cryptenamine has value in the chronic management of moderately severe hypertensive illness, notably in the individual with cardiac and retinal involvement and relatively intact renal function. Reserpine "priming" enhances the depressor response, and ameliorates side effects from cryptenamine.

Fatal Malignant Hypertension Following Prednisone Therapy of Diffuse Systemic Sclerosis

Burton M. Cohen, Elizabeth, N. J.

Interest has recently been focused upon the development of a "panmesenchymal reaction" in patients receiving adrenocortical steroid therapy. Hypertension has occasionally appeared in these patients concomitant with the use of steroids, usually when underlying impairment of renal reserve existed. It has been suggested that a relation of cause and effect may exist between the administration of steroids and the occurrence of malignant nephrosclerosis in some cases of rheumatoid arthritis, lupus erythematosus, and periarteritis nodosa.

Diffuse systemic sclerosis (scleroderma) is a mesenchymal disorder of obscure etiology with widespread visceral manifestations, as well as the more familiar cutaneous pathology. Although cardiovascular involvement is not infrequent, arterial hypertension is rarely seen unless hypertension of other origin or specific renal involvement is present. It is generally agreed that there is no specific therapeutic agent available at present which offers potential cure or prolonged arrest of this disease, although partial remissions have accompanied the use of adrenal and adrenocorticotropic hormones. Azotemia and malignant hypertension with fatal outcome have been noted sporadically in the literature in a limited number of patients with scleroderma under steroid management.

The case of a 51-year-old male with scleroderma of 3 years' known duration is described. Routine urinalysis and standard laboratory estimation of renal function were initially within normal limits, and arterial blood pressure at normotensive levels. Prednisone therapy over a 4-month period was marked by initial symptomatic remission, but was followed by a progressive rise in blood pressure (from 110–130/70–85 to 220/140) accompanied by a moderate weight gain, and nitrogen retention. Despite steroid withdrawal, death occurred due to massive cerebral hemorrhage. At autopsy there was membranous glomerulonephritis and lesions typical of malignant nephrosclerosis.

Hypertensive Arterial Disease and Aging

James Conway, Ann Arbor, Mich.

Attempts have been made to study the aging of arteries clinically in man and to determine its relation to hypertension. A test of arterial elasticity has therefore been developed which depends upon changes in pulse pressure which occur as the diastolic pressure is reduced immediately after the inhalation of amyl nitrite.

Using this test it has been possible to divide patients with hypertension into 2 groups. In 1 group hypertension appears to be associated with hardening of arteries, in the other it appears to be imposed upon a normal arterial system.

Hypertension associated with aging of arteries was the more common type and, on an average, the patients were older than those in the group with normal arteries. Observation of these patients suggests that the characteristics of the hypertensive disease are different in these 2 groups, particularly in regard to its severity, family history and response to treatment.

Cardiovascular Responses Following Chemical and Mechanical Stimulation of the Brain Stem via the Cisterna Magna

Edward S. Cooper, Sally Holm, Samuel Bellet, and Jose A. Sosa-Fantauzzi, Philadelphia, Pa.

The effect of medullary stimulation in dogs was studied chemically with KCl solutions administered

intracisternally and mechanically by needle puncture via the cisterna magna. The production of hypertension, various arrhythmias, and significant and marked RS-T segment elevation similar to that observed in myocardial infarction were observed. The mechanism of the production of these changes and methods by which they could be prevented and rapidly reversed were investigated.

Hypertension ranging from 200/140 to 430/230 was invariably produced in 30 dogs, and this could be prevented and reversed by hexamethonium but not by reserpine and phentolamine (Regitine). Arrhythmias usually coincided with the hypertensive effect following intracisternal KCl administration. However, arrhythmias were produced by minor mechanical stimulation without significant blood pressure rise. In the former group, reduction of blood pressure resulted in an abolition of the arrhythmias. In the latter group, the arrhythmias were abolished by hexamethonium without marked changes in blood pressure. Significant RS-T segment elevation and T wave inversion were observed after minor pricking of the brainstem. The RS-T segment elevation and T wave inversion with coving were similar to those observed clinically in subarachnoid hemorrhage. These changes are of considerable interest and at the present time are under investigation.

In summary, there are various mechanisms by which irritation and chemical injury to the brain stem may provoke hypertension, arrhythmias, and other types of cardiovascular changes. The mechanism of their production requires further elucidation.

New Radioisotope Technics for Measuring Coronary Artery Caliber

Eliot Corday, Henry L. Jaffe, Herbert Gold, and Lauro B. de Vera, Los Angeles, Calif.

Two radioactive isotope technics have been developed to measure the effect of various drugs and physical agents on the caliber of the intact coronary artery of the beating dog's heart. Both methods involve a negligible degree of trauma to the intact coronary artery, and can also be applied to almost any other accessible vessel.

Indirect Absorption Method. Fifty microcuries of P^{32} are encapsulated in polyethylene and this radioactive source is inserted underneath the left circumflex artery in the dog's beating heart. A miniature Geiger counter tube is fastened on top of the artery opposite the source of radiation. Since the blood in the artery will absorb or damp out the β rays, an increase in the caliber of the artery under investigation results in a decrease in the number of β radiations received by the Geiger counter, and vice versa. Thus the number of counts recorded is an inverse measure of the arterial caliber.

Direct Isotope Method. In this method, 4 to 10 μc. of P^{32} are injected intravenously in dogs. A lead shield is inserted under the intact coronary artery to screen out the background radiation from the heart. A miniature Geiger counter tube is attached to the surface of the coronary artery. With this method, the number of counts over a given point in the artery depends on the volume of blood passing beneath the counter. Therefore the number of counts rises as the vessel dilates and decreases as it contracts.

Using both technics, it has been clearly demonstrated that nitroglycerin and dihydropaverol hydrochloride injected intravenously are effective coronary dilators. These new technics offer great possibilities for the evaluation of the effects of pharmaceutical and physical agents on any accessible intact vessel.

Evaluation of Left Heart Failure: Comparison of Cardiac Catheterization Data, Valsalva Maneuver, and Indirect Measurements of Pulmonary Vascular Congestion

Richard S. Cosby, Lawrence M. Herman, Ellery C. Stowell, Jr., and Mary Mayo, Los Angeles, Calif.

Estimation of the degree of left ventricular failure is of vital importance in the evaluation of cardiac disease. In this respect the Valsalva maneuver is of immense diagnostic importance. Gorlin has described normal, intermediate and abnormal arterial pressure patterns. Our purpose in this communication is to evaluate the Valsalva maneuver as an estimate of pulmonary venous pressure, to describe transitional changes as failure recedes, and to describe a performance test in left heart failure, based on altered cardiopulmonary dynamics. Twenty-five patients at progressive stages of recovery from left heart failure were studied. Arterial pulse pressure curves during and following the Valsalva maneuver were recorded at varying levels of forced expiratory pressure. A work performance test consisting of mild exercise for 3 minutes followed. Oxygen consumption, ventilatory equivalent for carbon dioxide, alveolar and arterial pCO_2 and pO_2 were measured at rest, exercise, and for 20 minutes of recovery. The performance formula consisted of maximum oxygen consumption on exercise, ventilatory equivalent for carbon dioxide at rest, and ventilatory equivalent recovery time after exercise. Correlation of direct pulmonary venous pressure (cardiac catheterization) was possible in most cases.

Results. Four stages of the Valsalva maneuver represent decreasing degrees of failure, the "square wave" type, the stage of decreasing arterial pressure during strain, overshoot without bradycardia, and overshoot with bradycardia. An abnormal pattern may be "normalized" by increasing the forced expiratory pressure above 40 mm. Hg. This forced expiratory pressure is related to the height of pul-

monary venous pressure. The performance test correlates well with the Valsalva "stages" and has the advantages of greater sensitivity and more adequate grading.

Localization of Intracardiac Shunts by Two-Site Sampling

Milton G. Crane, John E. Holloway, Charles H. Sears, James A. McEachen, Ronald H. Selvester, and Ivor C. Woodward, Los Angeles, Calif.

Intracardiac shunts were localized using a new method. Radioiodinated serum albumin was injected through the distal orifice of a double lumen catheter, and blood samples were obtained from the proximal orifice of the catheter and from a brachial artery simultaneously. Indicator concentrations were determined by drawing the samples through separate well crystals and recording the activities continuously.

After the 2 recordings were calculated and corrected for the relative counting rates of the 2 channels and for the transit time from the point of sampling to the well crystals, direct comparisons could be made of the time of appearance as well as the concentrations of the indicator at the 2 sampling sites.

Left-to-right intracardiac shunts were detected on the arterial concentration curve by early appearance of recirculating indicator and were localized by determining that intracardiac sampling point at which indicator appeared sooner than that from the systemic circulation.

Right-to-left shunts were localized by selecting the site of injection such that early appearance of a portion of indicator was demonstrated on the build-up portion of the arterial concentration curve, similar to the report of Wood.

In 10 patients to date, left-to-right shunts were correctly detected and localized. With catheter sampling at or beyond the shunt, indicator appeared from 1 to 5 seconds before any appeared at the brachial artery. We observed that in the absence of shunts (or by sampling upstream from a shunt) indicator appeared at the right ventricle from 2 to 11 seconds *after* appearing in the brachial artery sample.

In 2 patients, concomitant left-to-right and right-to-left shunts were demonstrated and localized. These shunts were verified by other means.

Effect of Recirculation of Indicator on the Shape of the Arterial Concentration Curve

Milton G. Crane, John E. Holloway, Charles H. Sears, James A. McEachen, Clifford R. Anderson, and Ralph M. Adams, Los Angeles, Calif.

The effect of recirculating indicator upon the shape of the arterial concentration curve was studied by a new method. Radioiodinated serum albumin was injected through the distal orifice of a double lumen catheter in the MPA, and blood samples were obtained from the proximal orifice of the catheter and from a brachial artery simultaneously. Injections were also made in a cubital vein with sampling from the same sites as for the previous injection. The changing concentration of radioactivity in the 2 samples was determined by drawing the samples through separate well crystals and recording the concentrations continuously. If the 2 tracings are corrected for the relative counting rates of the 2 channels and for the time elapsed from the point of sampling to the well crystal, then direct comparison can be made of the time of appearance of the indicator as well as the relative concentrations at the right ventricle and brachial artery at identical instants of time. If the time base of the right ventricle concentrations is shifted to compensate for the transit time from right ventricle to brachial artery, then there is a direct measure of the time and quantity of the contribution that recirculation makes to the shape of the arterial tracing.

Fifteen patients were studied by this method. The results show that from 1 to 9 seconds of the exponential portion of the downslope (average 38 per cent) were affected by recirculating material. The recirculating material increased the sum of the concentrations of the curve to the point of obvious recirculation by 0.03 to 4.1 per cent (average 1.0 per cent). This effect on the exponential portion of the downslope resulted in an erroneous extrapolation of the downslope. Although the difference in slopes was from 0 to 23.4 per cent, the error in the area under the extrapolated portion of the curve was only 0.18 per cent.

Cardiac output values obtained after correction of the curve for contribution by recirculating material were from 0 to 3.9 per cent higher (average 0.8 per cent) than those obtained by the original curve.

Carcinoid Syndrome

James H. Currens and Howard Christian, Boston, Mass.

Three patients with the carcinoid syndrome have been observed at the Massachusetts General Hospital in the last 30 years. Two patients have come to autopsy; pulmonic stenosis was the predominant cardiac lesion in one and tricuspid insufficiency in the other. This report is of the last patient seen in the hospital and is the basis for the cinephotographs which were made of this patient during life.

A 55-year-old male was operated on in August 1948 because of abdominal pain; a malignant carcinoid was removed from the ileum. He was asymptomatic for 6 years when he returned to the hospital with mental confusion, a memory defect, and signs of congestive failure. Physical examination revealed a disoriented male with poor memory who dem-

st ated intermittent flushing. There was unusual pr ominence of the neck veins bilaterally with both a pr ominent superficial pulsation as well as a deep ju gular pulsation. No heart murmurs were heard. R serpine, 5 mg. intravenously, was given and gr atly aggravated the flush and resulted in transi nt diarrhea. Anasarca developed, and he died 9 m nths later. At autopsy the tricuspid valve was badly scarred, and there was fusion of the chordae te dineae. There was some scarring of the pulmonic valve, the right atrium was dilated, and the mitral valve was normal.

This film is primarily useful to demonstrate the flush that occurs in association with carcinoid syndrome as well as the cervical pulsations associated with tricuspid regurgitation. The anatomic cardiac abnormalities are well demonstrated in the film.

Use of the Strain Gage Arch as a Measure of Ventricular Function During Cardiopulmonary Bypass Operations

Thomas D. Darby, William H. Lee, Jr., John D. Ashmore, and Edward F. Parker, Charleston, S. C.

Although considerable variation exists among the groups utilizing cardiopulmonary bypass procedures for the surgical correction of intracardiac lesions, the basic principles as developed primarily by Lillehei et al. are generally followed. In the present studies the procedures were carried out through a right thoracotomy at the fourth intercostal space in the dog and through a bilateral transverse thoracotomy, anteriorly in the human. In all cases the venous cannulas were introduced into the superior and inferior venae cavae through 2 incisions in the right atrial appendage. In the dog, the arterial cannula was placed in the proximal end of the right carotid artery through an arteriotomy. In the human, the arterial cannula was placed in the distal abdominal aorta through a femoral arteriotomy. A DeWall type bubble oxygenator (Brunswick model) and Sigmamotor pump apparatus were used in all cases.

Direct continuous measurements of the changes in myocardial contractility were obtained by suturing a strain gage arch directly to the musculature of the right ventricule. The myocardium between the 2 sutures was stretched by 50 per cent of the initial diastolic length. For all practical purposes the contraction of the fibers between the 2 points of attachment is isometric. Factors which influence this method and the relationships of these recordings to other methods of measuring cardiac function have been published. Polyethylene catheters were placed in the brachial artery in the human and in the femoral artery of the dog for direct measurements of blood pressure by Statham pressure transducers. Frequent electrocardiograms were obtained during the procedure.

In the dog the results of these studies indicated that, following total occlusion of the venous return to the heart with flow rates of 35 to 40 ml. per Kg. per minute, there was little change in the force of contraction of the ventricular musculature. The time interval of total systole was shortened indicating a lesser work load on the heart. Following 10 minutes of cardioplegia, produced by potassium citrate, the early initial beats were generally reduced by 30 to 50 per cent of control values. However, the force of contraction usually returned to control levels if adequate flow rates had been maintained during the procedure. Upon release of the superior and inferior venae cavae there was usually an obvious cardiac dilation. A slight reduction in the contractile force recording (by approximately 20 per cent) and an increase in the time interval of systole usually accompanied this dilation. The duration of this phase of cardiac dilation was usually 4 to 8 minutes. In most instances in which contractility fell below pre-bypass control levels before cardioplegia, the contractile force during the recovery period remained below control levels.

In the patient, heart contractile force recordings served as a guide to determine adequate flow rates. Initial flow rates from 40 to 50 ml. per Kg. per minute were used. In most cases contractile force fell below pre-bypass levels before cardioplegia, whereupon the flow rates were increased by as much as 20 ml. per Kg. per minute. The contractile force was only slightly reduced following the procedure (approximately 12 per cent). The only obvious difference in the recordings of heart contractile force obtained from the patient and from the dog occurred in the contour of the curve. In patients with septal defects there was considerable notching and irregularity. However, after correction the curve usually resembled the curve obtained from the normal ventricle of the dog.

Place of Intracardiac Phonocardiography in the Diagnosis of Heart Disease in Man

George W. Deitz, Ali Ertugrul, Philadelphia, Pa., John D. Wallace, James R. Brown, Jr., Johnsville, Pa., and David H. Lewis, Philadelphia, Pa.

During the year since the presentation of preliminary results of intracardiac phonocardiography by our group, we have considerably amplified our experience with this technic. In addition to recording sounds at the time of right heart catheterization on 75 patients, sounds have been recorded from the systemic circulation by retrograde arterial catheterization. Sounds have also been recorded from the left side of the heart during cardiac surgery and by the occasional passage of the catheter through a patent foramen ovale.

Previous observations in dogs revealed that sounds from the left heart and aorta were louder than sounds from the right heart and pulmonary artery and that there was routinely a systolic murmur in the pulmonary artery and aorta. Studies in

man indicate that sounds from the left heart are louder than sounds from the right heart and that there is routinely a systolic murmur in the pulmonary artery but not in the aorta.

On the basis of experience thus far gained with this technic, intracardiac phonocardiography has proved to be of value in the following situations:

In rheumatic heart disease, exact localization of the site of production of murmurs has been obtained. For example, in tricuspid insufficiency there is a systolic murmur localized to the region of the tricuspid valve. In aortic stenosis and insufficiency, simultaneous recordings from pulmonary artery and aorta have revealed characteristic murmurs heard in the aorta but not in the pulmonary artery.

In acute pericarditis, there is a friction rub localized to the ventricle which can be heard even when no friction rub is heard on the chest wall.

In congenital heart disease, the ability of this technic to localize murmurs has given rise to a wholly new and valuable diagnostic tool. Characteristic murmurs, which in themselves have often been diagnostic, have been observed in patent ductus, ventricular septal defect, atrial septal defect, and pulmonary stenosis.

Pulmonary Dynamics in the Presence of Atresia of One Pulmonary Artery

John R. Derrick, H. Stephen Weens, and John M. Howard, Atlanta, Ga.

One of the rare causes of pulmonary emphysema is partial or total atresia of the pulmonary artery of the opposite lung. This condition is of importance in the differential diagnosis of other causes of pulmonary emphysema, as well as atelectasis of the affected side. The clinical diagnosis of this condition depends upon fluoroscopic observation of diminished pulmonary function, and an absent or diminished pulmonary artery pulsations on the involved side. Diagnostic confirmation of the condition is obtained by angiocardiography.

Two patients exhibiting varying degrees of pulmonary artery atresia have been studied by the technic of cineroentgenography. This procedure permits satisfactory demonstration of deficient function of the affected lung associated with the development of pulmonary emphysema, and mediastinal herniation on the unaffected side. The clinical and angiocardiographic findings in these patients will be briefly discussed, and a cineroentgenogram showing this entity will be presented.

Decreasing Caliber of the Superior Mesenteric Artery Associated with Aging

John R. Derrick, William D. Logan, and John M. Howard, Atlanta, Ga.

This study has been designed to provide an anatomic explanation for the physiologic changes of the gastrointestinal tract associated with aging and to survey the potential of a direct surgical approach to the major vascular problems of the superior mesenteric artery. Specifically, it has been a study of the effect of arteriosclerosis on the cross-sectional area of the lumen of the superior mesenteric artery in 50 humans. The cross-sectional area was calculated from the diameter measured in two different planes. This area was determined at the aortic orifice of the artery, at the narrowest segment of the artery which was invariably 0.25 to 1.0 cm. distal to the aortic origin, and 1.5 cm. distal to its origin. At the last point, the artery was usually free of arteriosclerotic changes. Inside diameters were measured from specimens obtained at post mortem.

Nineteen of the 50 aortas demonstrated a distinct narrowing of the superior mesenteric artery. This encroachment on the lumen varied from 12 to 86 per cent, with an average of 28 per cent. The narrowing did not occur at the origin of the artery but immediately distal.

In several instances, visceral ischemia might have been the etiology of the chronic gastrointestinal syndrome. Based on experiences in aortic resection and in the surgery of the brachial and popliteal arteries, surgical resection of the superior mesenteric artery, with restoration of continuity, would appear feasible. Such an operation need not necessitate resection of the artery's origin.

Interpretation of the Precordial Electrocardiogram from Right and Left Intracavitary Leads

Janet Dickens and Harry Goldberg, Philadelphia, Pa.

The discrepancies still apparent in electrocardiographic interpretation indicate the necessity for further studies of the activation of the human heart. Endocardial electrocardiography has been utilized in an attempt to clarify the mechanism and differentiation of right or left bundle-branch block from right or left ventricular hypertrophy, respectively. Six normal patients and 37 with congenital and acquired cardiac lesions were studied. Left and right ventricular endocardial complexes were obtained simultaneously in some cases by combined heart catheterization. A consistent group of patterns was obtained in the right ventricle in most cases, consisting of an RSR′S′ over the pulmonic valve, in the right ventricular outflow tract, and over the tricuspid valve, while an rS pattern was recorded in the mid–right ventricle. From these patterns and the simultaneously recorded precordial leads, a sequence of activation of the heart is suggested in which the R′ is attributed to upper septal activation, while the endocardial S′ reflects depolarization of the upper free right ventricular wall. The mode of activation of the heart is not altered in right bundle-branch block from the normal, since similar endocardial patterns are obtained

in all. Differences in the precordial electrocardiogram reflect differences in position of the heart with respect to the peripheral lead and the normal left ventricular predominance. In some cases of left ventricular hypertrophy on the routine electrocardiogram, the finding of an rS pattern in the left ventricle, simultaneously with a QS in the right ventricle, indicates the presence of left bundle-branch block. An R′ was not observed in the right ventricle in these cases. Comparison of the endocardial tracings was made with the type of lesion, age of the patient, right ventricular pressures, electrocardiographic, and vectorcardiographic findings. Unusual patterns were seen in several patients.

Disposable Screen Oxygenator

Gerald A. Diettert and Bernard A. Bercu, St. Louis, Mo.

It has been demonstrated that the stationary screen oxygenator (Gibbon lung) is an efficient and safe method for oxygenating blood in a high flow extracorporeal system. It is, however, an expensive, permanent piece of equipment; these factors have been a deterrent to its general use.

An inexpensive, disposable screen oxygenator has been designed and tested. Blood enters the top chamber, the floor of which is formed by aluminum bars of lengths of standard stock material. The blood films on 8 aluminum screens clamped between these bars. The surrounding case and top chamber are made of flexible plastic sheeting with plastic blood and oxygen tubes sealed in. The entire unit may be autoclaved. After use, the screens and case may be discarded. Only the aluminum bars and a stand used to support the assembled unit are reused.

Each screen will oxygenate approximately 300 ml. of blood per minute. The number of screens utilized may be reduced by simply omitting the aluminum screen between the bars during assembly.

The oxygenator has been utilized satisfactorily for circulatory support in a high flow extracorporeal system in a series of dogs.

Cardiovascular-Renal Effects of Isoproterenol in Congestive Heart Failure

Harold T. Dodge and Hershal V. Murdaugh, Jr., Durham, N. C.

Others have shown that isoproterenol increases strength of cardiac contraction and cardiac output in experimental animals and normal man.

This is a study of the cardiovascular-renal effects of intravenously infused isoproterenol (1–2 μg. per minute) for periods up to 1 hour in subjects with congestive heart failure. Right heart catheterization with measurement of cardiac output (Fick method), pulmonary arterial pressure, and brachial arterial pressure were performed in 8 subjects.

During infusion cardiac output increased in all subjects from a mean control cardiac index of 1.86 ± 0.59 L. per minute to 3.02 ± 0.43 L. per minute. A-V oxygen difference showed a mean decrease of 3.1 ± 1.2 volumes per cent from a mean control A-V oxygen difference of 8.9 ± 2.3 volume per cent.

Mean oxygen consumption increased 23 ± 16 cc. per minute and heart rate an average of 14 beats per minute. Stroke volume increased from a mean control value of 50 ± 12 ml. per minute to 70 ± 18 ml. per minute. Systemic arterial pulse pressure widened with little change in mean arterial pressure. Peripheral and pulmonary vascular resistance fell. Left ventricular work rose 76 ± 27 per cent from a mean control value of 5.90 ± 2.95 Kg. M. per minute and left ventricular stroke work 51 ± 24 per cent from a mean control of 81 ± 31 Gm. M. per beat. This increased left ventricular stroke work was associated with no change or a decrease in pulmonary arterial mean and diastolic pressures. Peripheral venous pressure fell in 2 subjects in which it was measured.

Renal clearances were performed in 7 patients. Urine flow increased 2 to 3 fold in 6. During infusion, GFR in 2 increased to normal values from mean controls of 30 and 65 ml. per minute with a proportionate increase in ERPF. Subjects with relatively normal control GFR showed no consistent change in GFR.

The positive inotropic effect of isoproterenol was observed whether the patients were receiving digitalis or not. These studies form a basis for another approach to the treatment of refractory heart failure.

Significance of Right Heart Strain in 400 Cases of Congenital Heart Disease: Hemodynamic and Electrocardiographic Correlation

Leonard Dreifuss, Sheldon Bender, Lamberto Bentivoglio, Daniel Downing, and Harry Goldberg, Philadelphia, Pa.

The failure to recognize consistently specific congenital cardiac anomalies electrocardiographically led us to examine the hemodynamic and electrocardiographic alterations in cases where right heart strain could be expected. One hundred cases each of atrial septal defect (ASD), ventricular septal defect (VSD), pulmonic stenosis (PS), and tetralogy of Fallot (Tet.) were studied.

An R/S–V_1 ratio greater than 1 was present in 94 per cent, ASD; 65 per cent, VSD; 74 per cent, PS; 93 per cent, Tet. An R/S–V_1 ratio of less than 1, and an R/S–V_6 ratio greater than 1, was seen in 5 per cent, ASD; 35 per cent, VSD; 26 per cent, PS; and 7 per cent, Tet. These 73 cases showed no evidence of right heart strain. A diagnosis of combined heart strain according to accepted criteria could be made in only 12 cases of VSD.

The following abnormal V_1 patterns were con-

sidered indicative of right heart strain: rSR′, RS, rR, slurred R, R, Rs, qRs, qR. Predominating QRS–V_1 patterns were: ASD–rSR (70 per cent); VSD–RS (40 per cent); Tet.–Rs (32 per cent); and R (19 per cent). No predominating V_1 pattern appeared in PS. Predominating QRS–V_6 patterns were: ASD–Rs or rS (81 per cent); VSD–qRS (69 per cent); PS–qRS (49 per cent); Tet.–rS (46 per cent); and qRS (32 per cent). QRS duration was significantly greater in ASD than in the other groups.

A correlation of QRS configurations in V_1 and V_6 with hemodynamic data in the various lesions proved unsatisfactory. The height of RV_1 showed no statistically significant difference, regardless of the lesion or right ventricular pressure.

The diagnosis of right heart strain can be made with reasonable confidence (84 per cent of all cases) when an abnormal QRS pattern is seen in V_1 with an R/S ratio greater than 1. On the other hand, the poor correlation of hemodynamic and electrocardiographic data with the frequent appearance of similar QRS–V_1 and V_6 patterns in all groups mediates against a specific anatomic or hemodynamic diagnosis.

Pressure Phenomena in the Partially Occluded Brachial Artery

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Studies were conducted on human subjects in whom Korotkoff sounds distal to a sphygmomanometer cuff wrapped around the arm were recorded through a phonocardiogram microphone, during inflation and deflation of the cuff, simultaneous with brachial artery pressures transmitted through an indwelling needle whose tip was 1 to 2 cm. distal to the cuff.

On elevation of cuff pressure sufficient to occlude arterial flow, brachial artery pressure decreased to a level between 15 and 50 mm. Hg. During subsequent deflation of the cuff, Korotkoff sounds and pulse waves of 2 to 10 mm. Hg occurred at a cuff pressure approximating systolic pressure.

During progressive deflation of the cuff while Korotkoff sounds remained audible, brachial artery pressure increased, until at some cuff pressure near mean pressure of the artery when not occluded, the systolic and diastolic pressures exceeded by 1 to 12 mm. Hg the respective pressures in the nonoccluded artery. The maximal increase in diastolic or mean pressure on partial occlusion of the brachial artery was found, with subjects in stable state, to be similar on repeated trials with varying gradations in deflation, similar for inflation or deflation of the cuff, and constant while cuff pressure was maintained constant; but was sensitive to changes in heart rate or vasomotor activity. The maximal diastolic gradient was less than 12 mm. Hg in most normal subjects at rest, increasing after administration of isoproterenol sublingually or epinephrine intramuscularly and when exceeding 12 mm. Hg, falling below that level after sublingual administration of nitroglycerin. In patients with aortic insufficiency the gradient was between 10 and 50 mm. Hg, falling slightly, if at all, on administration of nitroglycerin. This effect was considered due to a fall in central aortic diastolic pressure consequent to aortic regurgitation, which was not transmitted across the partially occluded brachial artery whose diastolic pressure reflected the peripheral vasomotor state and the gradient correlated with clinical estimation of the severity of aortic insufficiency.

Increasing Incidence of Liver Necrosis: Possible Relationship to Administration of Vasopressor Amines

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Previous experimental studies in animals have shown that a single intravenous injection of any one of the sympathomimetic amines may be associated with the development of diffuse vascular lesions. Cardiac lesions similar to those produced experimentally have been observed at postmortem examination in patients treated with vasopressor amines. These human lesions, however, present a difficult problem in evaluation, since cardiovascular diseases of many types produce similar alterations.

Liver necrosis of the type produced in experimental animals given vasopressors is said to be exceedingly rare in man, and therefore readily lends itself to an appraisal as regards its pathogenesis.

The autopsy protocols of 3,229 patients, examined between the years 1946 through 1955, were reviewed for evidence of liver necrosis. This survey revealed 62 cases of classic liver infarcts, or ischemic or hemorrhagic areas of necrosis. A striking, progressive increase in the incidence of liver necrosis was evident, 72 per cent of the 62 cases occurring in the years 1953–1955. Gross anatomic basis for the development of necrosis, such as vascular occlusion or trauma, was present in only 11 of the 62 cases. In 51 of these cases, or 82 per cent, no cause was evident at the time of postmortem examination to explain the presence of the lesions.

Of particular interest is the possible role of the sympathomimetic amines in the production of the hepatic lesions. Forty-three of the 51 patients, or 84 per cent, had been given vasopressor amines, some in large doses and over prolonged time intervals. The striking similarity of the human lesions to those produced in experimental animals with vasopressors, and the coincidence of the precipitous increase in liver necrosis with the general increase in the clinical usage of these substances, strongly suggests that this group of drugs may be an important factor in the pathogenesis of the hepatic lesions

Effects of Sympathomimetic Amines on Forearm Venous Distensibility, Pressure and Volume

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A venous pressure-volume curve obtained plethysmographically from a forearm expresses the volume to which the veins are distended by any transmural pressure between 0 and 30 mm. Hg. Since venous distensibility (VD) is the same in both arms, the *natural* venous volume (NVV) of the forearm is the volume coordinate of that point on the curve which corresponds to the measured venous pressure (VP) in the unencumbered forearm. NVV changes depend upon changes in either VD or VP, or both, of these functions.

Normal men were studied in the supine position with the forearm dependent. Observations on VD, VP and NVV were made before, during, and after intravenous infusions of epinephrine or norepinephrine, and before and after single intravenous injections of methamphetamine or methoxamine.

In each of 11 experiments, epinephrine chloride (15 μg. per minute) caused an increase in VP, a decrease in VD, and a fall in the group average NVV from 3.0 to 2.0 ml./100 cc. of forearm tissue. In each of 6 experiments, norepinephrine bitartrate (30 μg. per minute) caused an increase in VP, a decrease in VD, and a fall in the group average NVV from 3.0 to 2.1 ml. Similarly, in each of 5 experiments, methamphetamine hydrochloride (20 mg.) caused an increase in VP, a decrease in VD, and a fall in average NVV from 2.9 to 2.4 ml. In 6 experiments, methoxamine hydrochloride, in a dose (10 mg.) producing hypertension and bradycardia, uniformly caused increases in VP, but only very small decreases in VD and small and directionally inconsistent changes in NVV.

Under the conditions of these experiments, methoxamine had little effect on forearm venous distensibility or volume. Epinephrine, norepinephrine and methamphetamine regularly caused appreciable shifts of blood out of the forearm veins, even in the presence of increased distending pressure.

Anatomy of Collateral Circulation

Edward A. Edwards, Boston, Mass.

Long recognized concepts of the anatomy of collateral circulation need to be clarified in the light of recent angiographic and other data. Special attention must be paid to the definition of collaterals, the degree of vascular isolation of various parts, the collaterals in actual use, and their effectiveness.

Ultimate vessels lying distal to an occluded segment constitute a "distribution" system with respect to the occluded segment, rather than collaterals. A second vascular system, as in the lung, heart, or liver, constitutes a "supplementary" variety of collateral. It may be ineffective because of difference in pressure or content. Bypassing an organ may be harmful, as when systemic diversion prevents the liver from acting on portal blood.

One channel of an anastomotic system may be long or wide at the expense of the other vessels. With such "unbalance" (Schlesinger), occlusion of a "preponderant" artery occasions more ischemia than occlusion of the diminutive vessel.

The effectiveness of collateral systems depends on the size of the anastomoses, the pattern of disease as regards collateral involvement, the functional needs of the tissue, and the general factors affecting blood flow and blood content.

In at least one organ, the kidney, total necrosis is less harmful to the patient than survival of the organ with a reduced arterial or venous circulation.

Portions of the body vary in degree of vascular isolation, as much with respect to the veins as to the arteries. In some locations, valves oppose collateral flow until dilatation engenders incompetence.

Surgical Treatment of Partial and Total Anomalous Pulmonary Venous Drainage

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Anomalous pulmonary drainage has been encountered 8 times in our series of 60 patients with shunts at the atrial level. Partial anomalous pulmonary venous return in association with interatrial communications has occurred 6 times. One adult with an intact interatrial septum has been explored. Total anomalous pulmonary venous return was encountered once, and corrected.

Recognition of these malformations is of importance, since re-establishment of normal pathways of venous drainage can be achieved at the time associated atrial defects are treated.

Partial anomalous venous drainage, with or without associated atrial defects, cannot always be differentiated from isolated atrial defects with left-to-right shunts, although it may be suspected when the murmurs are atypical and when radiographic examination reveals evidence of increased pulmonary flow and/or abnormal venous channels.

Total anomalous pulmonary venous return can be recognized on the basis of the clinical findings, cyanosis, and the presence of a "venous collar" above the cardiac silhouette. The diagnosis of partial anomalous venous drainage was suspected in 5 of 7 patients after pulmonary veins from the right lung were entered by the catheter.

These patients were operated upon using hypothermia. An atrioseptopexy, with the creation of a third chamber to bridge the pulmonary veins and the atrial defect, was done in 4 patients. The superior vena cava was transplanted into the right atrium in 2 of these; an arterial graft was necessary once. An atrial defect was closed in 1 child, but his

anomalous drainage was not corrected. Pneumonectomy was done in 1 adult without an associated atrial septal defect. One child was explored only.

The total anomalous return was corrected by anastomosis of a common posterior chamber to the left atrium, division of a left superior cava, and closure of the atrial defect. Normal pulmonary venous drainage in patients with partial anomalous venous return can be achieved by modified atrioseptopexy.

Effect of pH Change on Renal Vascular Resistance and Urine Flow Rate

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The effect of acute pH change upon renal vascular resistance and urine flow rate was studied in 32 pentobarbitalized, laparotomized dogs. In a first series, blood flow was controlled with a pump interposed in the renal artery and pressures measured in the renal artery and vein. Blood pH was varied from 7.0 to 7.6 by ventilation with 20 per cent CO_2 followed by hyperventilation. Changes in total renal vascular resistance in nerve intact, denervated, and denervated phentolaminized kidneys were +0.43 ± 0.54, +0.82 ± 0.71, and +0.75 ±0.51 mm. Hg per ml. per minute. Physostigmine added to the latter preparation failed to alter the results. Resistance changes occurred predominantly on the alkaline side of pH 7.3, and were most regular in denervated kidneys. Urine flow rate changes were +0.49 ± 0.25, +0.28 ± 0.16, and +0.47 ± 0.41 ml. per minute, and were in the same direction as the arterial pressure. In a second series, urine flow rate and aortic pressure were measured without the blood pump. pH change 7.0 to 7.6 in nerve intact, denervated, and denervated phentolaminized kidneys was associated with urine flow rate changes of +0.02 ± 0.48, +0.22 ± 0.70, and +0.27 ± 0.58 ml. per minute. Corresponding changes in aortic pressure were +16 ± 13, +8 ± 11, and +7 ± 13 mm. Hg.

These data demonstrate that reduction of hydrogen ion concentration results in active renal vasoconstriction through some direct effect upon vascular smooth muscle. The change is less apparent in nerve-intact kidneys because of antagonistic vasodilatory effects mediated through extrinsic nerves. The antagonistic influences are less effective in controlling local resistance change in dog kidney than dog foreleg.

The experiments fail to demonstrate the mechanisms of diuresis following administration of acidifying salts, but do indicate that the diuresis is related to something other than a simple pH change. Primarily they indicate that pH is an important factor in determining renal vascular resistance and hence blood flow rate.

Effect of Heparin on the Total Oxygen Consumption of Atherosclerotic Individuals

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The total oxygen consumption and R.Q. was determined in 46 individuals with known coronary atherosclerotic disease using Douglas bags. The subjects were in the fasting state, rested for ½ hour before the collection of samples of expired air in a room maintained at a temperature variation of no more than ±1 C. Determinations were made prior to, and 2 to 10 minutes and 2 to 3 hours after the intravenous injection of 100 mg. heparin. Frequently 2 control samples were taken before heparin was given.

There was no change in oxygen consumption in 23 subjects (average control O_2 206 cc. per minute). There was an increase in total oxygen consumption after heparin greater than 10 per cent above control levels in 20 individuals (average control O_2 174 cc. per minute). This rise averaged 33.6 per cent (range 11 to 94 per cent), and usually did not occur (or was only partial) in the first 10 minutes after heparin. There was a decrease in oxygen consumption greater than 10 per cent in 3 subjects. This fall averaged 15.3 per cent (range 13 to 17 per cent). The results (20:3) are statistically significant. Saline placebos were administered under identical conditions at other times in 12 of the individuals showing increased oxygen consumption after heparin. This produced no effect or only a slight increase or decrease in oxygen consumption in 11 of the 12 patients. In 3 stable subjects who had increased oxygen consumption after heparin, with a negative placebo effect, the effect of heparin was restudied using a continuously recording technic (Pauling analyzer). The increase again occurred, became apparent in about 10 to 20 minutes, and remained at an approximate plateau for at least 2 to 3 hours when the observations were discontinued.

Possible mechanisms involved in this fairly marked increase in oxygen consumption after heparin in 43 per cent of coronary atherosclerotic patients will be discussed.

Regression after Open Valvotomy of Infundibular Stenosis Accompanying Severe Valvular Pulmonic Stenosis

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Open pulmonary valvotomy through the pulmonary artery under hypothermia has been employed at the New York Hospital since January 1956, because of the more complete relief of the valvular stenosis that this technic affords. During this time 3 patients, operated on for severe valvular pulmonic stenosis, were found to have only a partial reduction in right ventricular systolic pressure after the cone-shaped valve was incised out to the

alve ring. Systolic pressures in the right ventricle rior to valvotomy were 170, 175, and 178 mm. Hg nd postvalvotomy pressures were 90, 100, and 130 m. Hg.

Pressure measurements in the operating room ndicated an area of obstruction in the outflow ract of the right ventricle just proximal to the ulmonary valve. Visual and digital inspection of his region through the pulmonary artery revealed marked narrowing of the outflow tract during entricular systole and a widening as the muscle elaxed. At the time of valvoplasty it was deemed nwise to attempt infundibular resection under ypothermia.

During the subsequent 6 to 12 months of postoperative observation, signs of pulmonary stenosis have regressed. The pre- and postoperative findings on these patients, including progressive changes in the electrocardiogram and the findings on cardiac catheterization 1 year after operation, will be presented.

This form of infundibular pulmonic stenosis accompanying severe valvular pulmonic stenosis is attributed to the uniform marked hypertrophy of the right ventricular musculature and small size of the valve ring. The regression of this stenosis followed restoration of pulmonary valve function and decrease in right ventricular hypertrophy. Observations on these 3 patients imply that it is unnecessary to resect portions of the right ventricular outflow tract under these circumstances.

Comparison of the Effects of β-Sitosterol and Safflower Oil, Alone and in Combination, on Serum Lipids of Humans: Long-Term Study

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This study was designed to compare the action of β-sitosterol and safflower oil, alone and in combination, on serum lipids of humans. Safflower oil is a highly unsaturated vegetable oil containing 70 per cent linoleic acid, and virtually no linolenic acid, tocopherol, or phytosterol.

Fifteen outpatients, average age 48, were maintained on a constant intake of total calories (average 2,340) and fat (average 103 Gm.) for 40 to 52 weeks.

Phases I, III, V, and VII were control periods, with an average intake of 95 Gm. of animal and hydrogenated fat, and 11 Gm. of vegetable oil. Safflower oil, 81 Gm. per day, in substitution for animal fat or β-sitosterol, 18 Gm. per day, were given in random during phases II and IV. In phase VI, a combination of β-sitosterol and safflower oil was given. Each experimental phase lasted approximately 7 weeks.

Weekly serum samples were analyzed for total cholesterol, α-lipoprotein cholesterol (ALPC), and β lipoprotein cholesterol (BLPC) (method of Anderson and Keys). Pooled samples were analyzed for total lipids (method of Bragdon), and for phospholipids. Triglycerides were calculated by difference.

The results revealed a rapid and sustained decrease in serum total lipids, phospholipids, cholesterol, and BLPC. Changes in ALPC and serum triglycerides were not significant. The average fall in BLPC was 46 mg. per 100 ml. (20 per cent) following β-sitosterol, 47 mg. per 100 ml. (20 per cent) following safflower oil, and 71 mg. per 100 ml. (32 per cent) after the combination of the two. Average body weight varied less than 1 Kg. throughout all periods. ALPC and BLPC values varied less than 3 per cent during the 4 control periods.

The results confirm previous findings on the action of β-sitosterol in humans and reveal that changes of a similar magnitude occur when safflower oil is given in substitution for animal fat. The magnitude of the decrease with the combination, although not additive, was 60 per cent greater than that observed with either agent alone. It is concluded that the effect of safflower oil upon serum lipid concentration depends largely on factors other than its content of sitosterol.

Oral Prophylaxis Maintenance in Rheumatic Children: Technics for its Evaluation and Results

Alvan R. Feinstein, Jeanne A. Epstein, Rita Simpson, and Harrison F. Wood, Irvington-on-Hudson, N. Y.

Oral and injectable agents are now being widely used to prevent streptococcal infections in rheumatic children. In comparing the intrinsic effectiveness of these agents, it is of crucial importance to determine how faithfully oral prophylaxis has been maintained.

For this purpose the casual questioning of patients by different physicians at routine clinic visits is often unsatisfactory. Hence, 2 separate technics were employed at the Irvington House Prophylaxis Clinic, where a group of 400 rheumatic children are seen every 4 weeks in a carefully-controlled, statistical study of 3 prophylactic agents: oral sulfadiazine (1.0 Gm. per day), oral penicillin (200,000 U. per day), and injectable benzathine penicillin (1.2 million U. per 4 weeks). Each child taking oral prophylaxis was given a 10 to 15 minute interview by the same physician and asked a series of specially-prepared questions designed to enable a classification of prophylaxis fidelity. Simultaneously, a second approach sought to obtain more objective data by providing each child with known amounts of the prophylaxis medication in bottles whose residual tablets were returned and carefully counted at each clinic visit. Disadvantages in both technics were recognized, but no more desirable methods

seemed applicable for large-scale screening of this type.

From the physicians' interviews, prophylaxis was considered "good" if less than 5 daily, nonconsecutive doses were missed per month and if the history was believed to be reliable. By these criteria, 73 per cent of the 113 patients receiving oral penicillin and 67 per cent of the 126 patients on sulfadiazine maintained "good" prophylaxis. During the first 3 years of the study, streptococcal infections occurred in 29 per cent (24/82) of the "good" and 52 per cent (16/31) of the "not-good" oral penicillin group and in 20 per cent (17/84) of the "good" and 50 per cent (21/42) of the "not-good" sulfadiazine group. (In the patients receiving monthly benzathine penicillin injections, 12 per cent (14/116) had had streptococcal infections.)

Using the pill-count method, prophylaxis was considered "good" if the returned number of tablets closely approximated the anticipated value. In certain children evaluation was difficult because bottles were either not returned or contained too few tablets (presumably due to destruction of the medication or to its use by other members of the family). From these data, a definite classification of "good" prophylaxis maintenance could be made in 55 per cent of the penicillin and in 44 per cent of the sulfadiazine group. Although the percentage of "good" patients was lower by this technic than by the interview method, the incidence of streptococcal infections was similar in the "good" groups of both methods. Of the patients considered "good" by the pill-count survey, streptococcal infections occurred in 27 per cent (16/60) of the oral penicillin group and in 21 per cent (11/53) of those receiving oral sulfadiazine.

The technics evolved appear to be useful methods in studying the difficult problem of oral prophylaxis fidelity in large clinic groups.

Bipolar Chest Leads in the Electrocardiographic Diagnosis of Left Ventricular or Atrial Hypertrophy in Children

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Using standard 12-lead electrocardiograms, it is difficult to determine left ventricular hypertrophy (LVH) in children because the usual S-T segment and T wave changes are often absent, and the diagnosis frequently depends solely upon the interpretation of excess precordial voltage. Similarly, the ECG diagnosis of atrial hypertrophy (AH) often involves troublesome measurement of P wave duration, since gross notching, peaking, and broadening may not be present.

In an effort to obtain more definitive ECG evidence of LVH and AH, bipolar chest lead tracings were correlated with the standard 12-lead records and with the clinical and roentgenoscopic data in a group of rheumatic children and in several with congenital heart disease. After various locations were explored, the most satisfactory selection of bipolar tracings were found in 4 positions. Of these, the most useful appeared to be a "sagittal" lead, taken between the second interspace at the right sternal border and the left scapular tip.

In 32 children (ages 5 to 17) with no heart disease, both standard 12-lead and bipolar tracings were essentially normal. In 36 children with heart disease and left ventricular enlargement, standard tracings showed the classical pattern of LVH (excess voltage plus ST-T changes) in 8; 12 had only excess precordial voltage; 2 had only depressed S-T segments; 4 showed borderline voltage; the remaining 10 were normal. The "sagittal" bipolar lead showed S-T segment depression in 7 of the 8 whose standard tracings showed LVH and in 19 of the 28 individuals whose standard tracings were either normal or only suggestive. In the latter group, the "sagittal" lead thus enabled the ECG diagnosis of LVH.

In many instances of atrial enlargement, the bipolar leads showed an abnormal P wave amplitude which was more easily discernible than the corresponding prolonged duration seen in the standard tracings. In 44 children with roentgenoscopic atrial enlargement, 16 showed P wave abnormalities in both standard and bipolar leads, 3 had abnormal standard records but normal or borderline bipolar chest tracings, while 4 demonstrated unequivocal P wave abnormalities only in the bipolar leads. The addition of the bipolar chest leads thus did not augment the ECG diagnosis of AH with the same consistency and utility as the single "sagittal" lead aided the determination of LVH.

The frequency with which S-T segment abnormalities appeared in the "sagittal" lead of children with left ventricular enlargement and borderline or normal standard ECGs indicates the utility of this lead in the routine electrocardiographic evaluation of children with suspected heart disease. Other bipolar chest leads may also help in the diagnosis of AH and in the vectorial analysis of P and QRS complexes.

Cure of Subacute Bacterial Endocarditis with Oral Erythromycin Alone after Failure of Penicillin, Streptomycin and Tetracycline

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Erythromycin has generally been considered ineffective in the treatment of subacute bacterial endocarditis unless it is given parenterally and in combination with other antibiotics. The importance of the case reported here is its demonstration of a cure of subacute bacterial endocarditis with oral erythromycin alone. In this instance the drug was used after penicillin, penicillin with streptomycin, and tetracycline had failed.

A 12-year-old boy with established rheumatic

mitral and aortic valve disease was admitted to Irvington House for convalescence from what was considered to be his third attack of rheumatic fever, the first having occurred, with residual heart damage, at age 6. On admission he was found to be persistently febrile, with tachycardia, heart murmurs, no petechiae or splenomegaly, and an elevated sedimentation rate and CRP. This was assumed to represent rheumatic activity and meticorten therapy was begun. After 5 days, it was stopped when the pretherapy blood culture was reported positive for streptococcus viridans. Intramuscular penicillin was given at 900,000 U. daily for 1 week, was raised to 10,000,000 U. per day for the next 2 weeks, and then was kept at 10,000,000 U. per day together with 1.0 Gm. of streptomycin for the next 10 days. During this time, the patient remained febrile, and numerous blood cultures were all positive.

Penicillin and streptomycin were stopped, and oral tetracycline 2 Gm. per day was begun. Nine days later it was discontinued because blood cultures had remained positive. Oral erythromycin, 2.75 Gm. per day, in divided doses was then instituted. The patient became afebrile on the following day. A blood culture taken 3 days later, and all remaining blood cultures thereafter showed no growth. The erythromycin was continued for 8 weeks, then stopped. Under observation for the next 6 months, the patient has shown no clinical or laboratory evidence of recurrence.

Corrected Transposition of the Great Vessels Associated with Intracardiac Defects

Burton W. Fink, Forrest H. Adams, Russell A. McFall, and Bernard J. O'Loughlin, Los Angeles, Calif.

The purpose of this report is to describe a poorly understood congenital malformation referred to as "corrected transposition of the great vessels" and to show how it can be differentiated from simple interventricular septal defect with a left-to-right shunt, and from true transposition of the great vessels. Four patients were studied by cardiac catheterization and selective angiocardiography; 2 of these were explored surgically. One patient expired and has been studied at postmortem examination.

In all of the patients, the course of the cardiac catheter was medial and somewhat posterior as it entered the pulmonary artery from the right ventricle. Likewise, all had a significant left-to-right interventricular shunt with right ventricular and pulmonary hypertension. Selective angiocardiography demonstrated the anatomic position of the pulmonary artery and the aorta in each case.

Autopsy examination in the 1 patient demonstrated the transposed nature of the atrioventricular valves and of the ventricular musculature on the 2 sides.

Proper clinical recognition of corrected transposition of the great vessels associated with an interventricular septal defect is essential, now that corrective surgery is possible for simple interventricular septal defect. It is possible to make such a diagnosis by the combined use of cardiac catheterization and selective angiocardiography.

Right-Heart Catheterization in Infants and Children: Analysis of 218 Patients

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Advances in the technics of right-heart catheterization in infants and children make it desirable to appraise periodically the value of this procedure. From 1955 to 1957, 218 right-heart catheterizations in this age group have been performed at the UCLA Medical Center. The majority of these were performed by heart trainees under the supervision of the attending pediatric cardiologist. The present study was designed to determine the ease with which the procedure can now be performed, the accuracy of the results obtained, and the risk involved.

Of 84 infants under 2 years of age, either the aorta or the pulmonary artery (depending upon the type of anomaly) could be entered in 76 per cent of the cases (63 patients). Beyond this age, it was possible to enter these structures in 85 per cent of the cases (86 of 134 patients). Six infants under 2 years of age, and 16 older children, were proved at surgery to have a patent ductus arteriosus. The ductus was cannulated during catheterization in 5 of the former (83 per cent), and in 13 of the latter (81 per cent).

Using the findings of surgery as the correct diagnosis, the original clinical impression was confirmed in 57 of 77 patients (74 per cent). When the original clinical impression was supplemented with the catheterization data, the degree of accuracy increased to 91 per cent (70 of 77 cases).

Of the 218 patients, there was 1 death which could be directly attributed to the procedure. This occurred in a 10-year-old child who had an extensive myocardial infarction resulting from an unrecognized coronary occlusive process of long standing.

The authors conclude that right-heart catheterization may be performed in infants as well as older children, with a high degree of success and a reasonably low-risk rate.

Pressor Phenomenon Associated with the Postpartum State

Frank A. Finnerty, Jr., Joachim H. Buchholz, and Robert L. Guillaudeu, Washington, D. C.*

Recent experience in a Toxemia Clinic has shown that the period 2 to 20 weeks postpartum is frequently associated with asymptomatic hyperten-

sion. Serial studies on 2,311 patients have shown the sequence of an entirely normal past history, prenatal course, delivery, and immediate postpartum course with the first occurrence of an elevated arterial pressure at 2 to 7 weeks postpartum in 133 patients. Although multiparity predominated (average, 5 pregnancies), the average age of the group was 28 years. Mean arterial pressure increased from an average of 92 mm. Hg, to 120 mm. Hg, a 24 per cent average increase. Physical examination and routine laboratory studies, including careful ophthalmoscopic examination, x-ray of the chest, urinalysis, and electrocardiogram, revealed no other evidence of vascular disease.

Hospitalization in 15 patients (including 72 hours bed rest) was associated with only a 10 per cent decrease in mean arterial pressure. Response to ice, tilting, methanesulfonate, and histamine was not abnormal. Cardiac output and renal blood flow determinations were normal. The average duration of the hypertension was 12 weeks (7 to 42 weeks).

That some as yet undefined pressor mechanism exists during the postpartum period seems probable, since (1) serial studies on 1,130 hypertensive patients (history of hypertension prior to pregnancy) have shown the highest level of arterial pressure recorded during this period in 331 patients; (2) studies on patients followed through multiple pregnancies have shown the recurrence of transitory hypertension only during the postpartum period in 30 patients; and (3) studies on 4 patients with transitory hypertension recorded only postpartum currently show persistent hypertension.

The first occurrence of an elevated blood pressure postpartum is a rare phenomenon occurring in only 1 per cent of normal postpartum patients. A pressor phenomenon associated with the postpartum state is common, however, since in addition to the 133 patients with postpartum hypertension, 331 patients with a history of hypertension prior to pregnancy showed the highest level of arterial pressure postpartum. In summary, 20 per cent of patients who exhibited any pressor phenomenon in relation to pregnancy showed the highest level of arterial pressure during the postpartum period.

Evidence for an Extravascular T-1824 Space

Frank A. Finnerty, Jr., Joachim H. Buchholz, and Robert L. Guillaudeu, Washington, D. C.*

Previous studies in this laboratory have shown that acute reduction of arterial pressure in some hypertensive patients was followed immediately by a greater increase in plasma volume than could be accounted for by the decrease in hematocrit or plasma protein. With the hope of finding an explanation for this discrepancy, the reverse experiment, i.e., acutely elevating the arterial pressure, was performed.

Simultaneous determinations of plasma volume (T-1824) and red cell mass (Cr^{51}) in 10 patients before and during noradrenalin revealed: 1. The whole blood volume calculated from the plasma volume under control conditions was 5.1 L. (26 per cent) greater than the whole blood volume calculated from the plasma volume. 2. An average increase in mean arterial pressure from 98 to 150 mm. Hg (40 per cent average increase) was associated with a decrease in plasma volume from 3.3 to 2.8 L. (16 per cent average reduction), no significant change in the red cell mass, an increase in the hematocrit from 40 to 43 per cent (8 per cent average increase), and an increase in plasma protein from 6.5 to 6.9 Gm. per 100 ml. (6 per cent average increase).

These findings suggest that the T-1824 space might measure something different from the plasma volume and would be in keeping with the recent work of Vidt and Saperstein, and others, who feel that some of the T-1824 space may be extravascular. Since the red cells are confined by the capillary endothelium, they do not have access to the extravascular T-1824 compartment. An increase or decrease in the extravascular T-1824 compartment, therefore, would not be reflected by a change in hematocrit or plasma protein. In this way the hemoconcentration associated with noradrenalin could theoretically eliminate the extravascular T-1824 space and decrease the intravascular T-1824 space. Only the decrease in the intravascular T-1824 space would be reflected by an increase in the hematocrit and plasma protein, thus accounting for a greater change in the T-1824 space than in these strictly intravascular parameters. Such a hypothesis might also be used to explain the data found in the reverse experiments, i.e., acutely reducing the arterial pressure in some hypertensive patients. These mirror image results considered in conjunction with the present experiments seem to add evidence to the hypothesis that the T-1824 space measures something more than the circulating plasma volume.

Ventricular Pre-excitation (WPW) in the Presence of Bundle-Branch Block

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Occurrence of ventricular pre-excitation (WPW) in patients with bundle-branch block (BBB) appears to be extremely rare. A review of the literature revealed only 5 instances illustrated, without any comments concerning the implications of this unusual combination. A study of 3 recently observed cases, 2 of which will be presented, provided an opportunity to analyze circumstances which permit or prevent simultaneous manifestation in the electrocardiogram of the 2 types of abnormal ventricular activation. In the first case, pre-excitation was superimposed on a right BBB; in the other, on an intermittent left BBB which, in addition, was

complicated by a first degree A-V block. The diagnosis of pre-excitation was based in both cases on the presence of a typical delta wave, associated in the first case with an abnormally short P-R interval, in the second with foreshortening of a prolonged P-R to a "normal" one. In the first instance, typical features of right BBB were preserved during the pre-excitation, in the other the characteristics of left BBB disappeared with the onset of pre-excitation. In the latter case, comparative measurements of P-S intervals in control and pre-excitation tracings were possible, both in the presence and in the absence of left BBB. These revealed that, due to the depression of ordinary A-V conduction pathways, the pre-excitation impulse activated both the blocked and unblocked ventricles, thereby masking the severe intraventricular conduction defect.

We conclude that (1) pre-excitation may coexist with either a right or left BBB; (2) whether or not a BBB will be obscured by pre-excitation depends on the location of the A-V bypass relative to the site of the bundle-branch lesion, as well as on the state of conductivity in the normal A-V junction.

Study of the Manifestations of Rheumatic Fever Following Cessation of Therapy

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The cessation of hormone or salicylate therapy for rheumatic fever is frequently associated with the appearance of manifestations of rheumatic activity. The period immediately following cessation of therapy was examined in 257 patients treated in the United States and Canada as part of the Cooperative Study on the Management of Rheumatic Fever. For the purpose of describing the post-therapy period, the manifestations of rheumatic activity were studied irrespective of the treatment groups. The signs charted include, in order of frequency, abnormal ESR, fever, prolonged P-R interval, arthritis, erythema marginatum, congestive failure and/or pericarditis, nodules, and chorea.

Of the 257 children, 67 had none of the above manifestations of rheumatic activity following therapy. One hundred ninety patients exhibited 1 or more manifestations: 90 patients exhibited only 1 manifestation; 65 patients, 2 manifestations; 25, 3; 7, 4; and 3 had 5 manifestations. There were 34 different combinations of the various manifestations, many of which might not be acceptable as diagnostic of rheumatic fever in the absence of the previous history.

The number of manifestations exhibited during this period was greater in those patients: (a) with congestive failure and/or pericarditis on admission; (b) with a history of previous rheumatic heart disease; and (c) who were treated late in the course of their illness. It is not known whether the latter observation is due to selection or other factors.

The manifestations of the post-therapy period varied widely in severity. In most instances, abnormalities subsided spontaneously. In 10 patients congestive heart failure and/or pericarditis occurred; 4 of these did not have this manifestation on admission.

There is no reason to believe that the manifestations of rheumatic fever occurring in the post-therapy period are not directly related to the underlying disease. These manifestations are sufficiently common under conditions of good management to warrant the careful appraisal of this period in studies designed to investigate the therapy of rheumatic fever.

Retrograde Arterial Left Heart Catheterization, with Nonfluoroscopic Venous Right Heart Catheterization

Don L. Fisher, Pittsburgh, Pa.

The dangers of retrograde catheterization through the aortic valve can be minimized by special precautions. The use of a looped tip and the avoidance of prolonged runs of ventricular ectopic beats are the most important measures. A series of 25 patients with aortic and mitral valve lesions were studied by this method. The results were compared with those in a similar concurrent series of 25 patients having combined left and right heart catheterization by means of left and right atrium needle punctures.

For retrograde left heart catheterization, access of a radio-opaque catheter to peripheral arteries was gained by a modified percutaneous Seldinger method (flexible metal guide), or through a thin-walled arterial needle. The catheter was then advanced to the left ventricle and left atrium with fluoroscopic guidance, both the pressure and electrocardiogram being monitored continuously on a 2-channel oscilloscope. For simultaneous right heart catheterization, percutaneous access to peripheral veins was usually through an 18-gage thin-walled needle, the nonradio-opaque PE-50 polyethylene catheter being advanced to the right ventricle or pulmonary artery without the use of fluoroscopy. Direct Fick cardiac output was then measured, and pressures were recorded from right and left heart circuits.

A direct method of demonstrating either aortic or mitral regurgitation of blue dye was found useful, employing a double-lumen retrograde left heart catheter. Other advantages of the retrograde method may include greater convenience of access and less risk of complications than with other types of left heart catheterization. However, the method is not applicable in severe valve stenosis.

The percutaneous nonfluoroscopic venous right heart catheterization method may prove useful in special circumstances requiring either an unusually prolonged maintenance of catheter position, avoid-

ance of skin incision, or avoidance of radiation. A disadvantage of the method is the difficult passage in cases having tricuspid regurgitation.

Incidence of Combined Arteriosclerosis in the Arteries of the Brain and the Heart

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The report of the Committee on Anticoagulants, with its study of 1,031 cases of myocardial infarction, has been analyzed from the point of view of cerebral vascular accidents, before the infarction occurred and while under treatment for the myocardial infarction. This analysis discloses that many patients had simultaneous cerebral vascular disease.

The cerebral vascular disease study, which is now being conducted on our service, has been analyzed from the standpoint of the incidence of coronary artery occlusion in these patients. This analysis indicates that many patients with cerebral vascular occlusions also have coronary artery disease. The literature on these subjects and related fields has been reviewed, including the recent pathologic studies by Young, Gofman, Malamud, Simon, and Waters.

The interrelationships of arteriosclerosis in the 2 different sets of arteries will be discussed. From a pathologic, as well as a clinical analysis, there is a highly significant positive correlation between disease in the 2 artery systems. Experiences with anticoagulant therapy in the treatment and prophylaxis of both interrelated conditions will be discussed.

Clinical Application of a New Dye for Continuous Recording of Arterial Dilution Curves Independently of Variations in Blood Oxygen Saturation

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Accurate characterization and localization of intracardiac defects and of valvular heart lesions by means of indicator-dilution curves have become an important diagnostic technic. Variations in blood oxygen saturation interfere with the recording of such curves from the right heart or venous circulation when oximeters and densitometers in conjunction with Evans blue or similar dyes are used. Similar interference occurs in recording of dilution curves from the arterial circulation in subjects breathing room air and in patients with large right-to-left shunts. A new water-soluble tricarbocyanine dye (dye II) with a high spectral absorption at 800 μ, a wavelength at which oxy- and reduced hemoglobin transmit light equally, has been developed to circumvent these difficulties. Animal studies have shown dye II to be nontoxic and satisfactory for determination of cardiac output. It is bound to plasma proteins, but loss of the dye from the circulation is more rapid than Evans blue. Dilution curves were recorded simultaneously by oximeters at the ears and at a radial artery after successive injections of Evans blue and dye II into the same site in the heart and great vessels in 17 patients with congenital heart disease. There were no detectable toxic effects or visible skin discoloration. In 13 patients with no or only a small right-to-left shunt, analysis of the contours of the curves recorded successively at the radial artery showed them to be closely similar. In 4 patients with large right-to-left shunts, interpretation of the Evans blue curves was difficult or impossible due to variations in arterial blood oxygen saturation. The associated dye II curves were undistorted and aided considerably in establishing the correct diagnosis. In addition to its usefulness in the diagnosis of cyanotic heart disease, this dye bears promise for investigations during hypoxia and in applications of dilution technics in venous blood.

Enhancement of Antihypertensive Activity with Chlorothiazide

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It has been known for some time that salt depletion enhances the hypotensive effect of antihypertensive agents. Attempts in this clinic to take advantage of this effect using oral mercurials and carbonic anhydrase inhibitors were not sufficiently successful to warrant widespread application. The recent availability of chlorothiazide, a potent agent for increasing the excretion of sodium and chloride, prompted us to reinvestigate this problem.

Chlorothiazide was added to the regimen of 20 nonedematous, hypertensive patients already under treatment with ganglionic agents (mecamylamine, chlorisondamine or pentolinium), and, usually, rauwolfia. The dosage of chlorothiazide orally was 1.5 Gm. daily for 3 days followed by a maintenance dose of 1 Gm. daily. Observations have been carried out for an average period of 4 weeks. No side effects or evidence of electrolyte depletion have occurred at this dosage level. Following an initial weight loss of 1 to 2 Kg., body weight usually returned toward normal. However, there was a maintained, *additional* reduction of mean $\left(\frac{\text{systolic} + \text{diastolic}}{2}\right)$ blood pressure averaging 13 per cent, and a reduction of dosage requirement of the blocking agents averaging 40 per cent. In order to avoid hypotensive reactions, particularly postural hypotension, dosages of the blocking agents were reduced in half at the time chlorothiazide was begun and then further modified to obtain optimum effects. Results in smaller series suggest that chlorothiazide enhances the antihyper-

ensive effects of rauwolfia-hydralazine and rauolfia-veratrum combinations and also may restore he antihypertensive effect of surgical sympathecomy.

Balance studies indicate that in the dosages used he hypotensive response is accompanied by some epletion of body stores of sodium, potassium, and hloride without significant changes in plasma conentrations of these electrolytes.

The present results suggest that, over the short erm at least, chlorothiazide provides a practical, linical method for sensitizing the patient to various ntihypertensive procedures.

Effects of Cigarette Smoking on the Normal Male Peripheral Circulation, Utilizing Multitechnical Procedures

Jack Freund, Richmond, Va.

The physiologic effects of sham and actual cigarette smoking on the normal male peripheral circulation were studied with multitechnical procedures (skin temperature, digital plethysmography, radiosodium skin clearance, and A-V difference of oxygen saturation and lactic acid). The objectives of these studies were to determine the quality and quantity of tissue change measured by these procedures.

Careful statistical analyses were made of 419 records obtained in 32 experiments on 14 subjects. The results obtained were then correlated to determine the factors responsible for these effects.

No changes were observed to be statistically significant with any of the tests following sham smoking. The results with plethysmography which were significant when the entire population was studied were not considered a valid index of individual response, since the individual variability with plethysmography was found to be great. A significant fall in skin temperature, decrease in venous oxygen saturation and prolongation of clearance of radiosodium were observed. Although a decrease following sham smoking was suggested in the latter test, this did not fall beyond chance probability. A significant increase in pulse rate was observed following smoking. There was no correlation between the change in pulse rate and the results obtained with plethysmography. There was no significant change in either arterial or venous lactic acid following sham or actual smoking as compared to the control observations.

In summary, a significant reduction in peripheral skin temperature, radiosodium clearance, and venous oxygen saturation was observed in normal males after cigarette smoking. This was associated with an increase in pulse rate and marked individual variability with digital plethysmography. There were no significant changes observed following sham smoking.

Therapeutic Resolution of Experimental Atherosclerosis

Meyer Friedman and Sanford O. Byers, San Francisco, Calif.

Hypercholesterolemia was induced in 21 rabbits for a period of 3 months by high cholesterol feeding. The animals were then allowed to become normocholesteremic by removal of cholesterol from their diets. Seven of these normocholesteremic rabbits were sacrificed, and the degree of atherosclerotic involvement of the aorta was assessed by inspection and chemical analysis. The remaining 14 rabbits were paired according to the degree of hypercholesteremia observed during the previous period of hypercholesteremia.

One member of each pair (i.e., 7 rabbits) received a suspension of mixed phosphatides (5 per cent) by intravenous infusion for 6 hours approximately 3 times a week for a maximum of 6 weeks. The other members of the 7 pairs (controls) received infusion of dextrose (5 per cent). All animals were then sacrificed, and the aorta and coronary arteries were studied by inspection (gross and microscopic) and by chemical analysis.

A marked reduction in the degree of atherosclerosis of both the aorta and coronary vasculature was observed in the 7 rabbits treated with phosphatide infusions. Thus, although the aortic atherosclerosis was judged as 4.9 in the 7 control rabbits (grading 0 to 5) sacrificed before treatment and 4.7 in the 7 additional control rabbits receiving only dextrose, it was only 2.4 in the 7 rabbits treated with phosphatides. On chemical analysis, the average cholesterol content of the aorta of treated animals was found to be approximately 30 per cent less than that of the control animals. Histologic examination of the coronary arteries revealed a similar percentile reduction of atherosclerotic involvement in the treated as compared to the control animals.

It is believed that in the use of intravenous infusions of phosphatides a means now is available to effect a marked resolution of a previously existing atherosclerotic infiltration.

Cardiovascular Responses to Transcranial Electric Stimulation in Man and in the Dog

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Transcranial electric stimulation as administered, for example, in electroconvulsive therapy, is a neurogenic stressor profoundly affecting the cardiovascular system. The most prominent circulatory responses so induced are disturbances in the initiation and conduction of the cardiac impulse, and paroxysmal changes in arterial pressure. Because

these responses appear to be identical in man and in the dog, animal studies are useful in elucidating the underlying mechanisms. This is a matter of practical as well as theoretical interest in view of the fact that acute circulatory disturbances are the leading cause of death in electroconvulsive therapy (modified and unmodified).

Human Studies. ECT, modified by intravenous barbiturate anesthesia, myoneural blockade and 100 per cent oxygen, was administered to 36 adult psychiatric patients (405 treatments). Continuous electrocardiographic observations (except during electric stimulation) and frequent sphygmomanometric pressure determinations were made during each treatment.

Arrhythmias of varying degrees of severity occurred in 135 treatments (33 per cent). These arrhythmias are vagal and extravagal. Vagal arrhythmias are uniformly preventable by adequate atropinization. Treatment-induced pressor responses are reduced to one half their usual magnitude by prophylactic use of tetraethylammonium chloride.

Dog Studies. Transcranial electric stimulation was applied under comparable conditions, including continuous electrocardiography, to dogs. Blood pressure, however, was recorded directly from a cannulated carotid artery with a Statham transducer and Sanborn Polyviso. Direct recording revealed a transient fall in blood pressure occurring immediately after stimulation. This fall, presumably too brief to be detected in the human measurements, was abolished by atropine or TEA. TEA also exerted a partial protection against the blood pressure rise similar to that noted in humans. Phentolamine or phenoxybenzamine, however, completely blocked this pressor response.

Arrhythmias resulting from transcranial stimulation were similar to those in man. When electric stimulation was repeated at 15-minute intervals, there was a marked amelioration of arrhythmic activity with these successive stimulations. This suggests depletion of some unidentified substance.

New Approach to Analysis of Variations in T Wave due to Change in Cycle Length

Manuel Gardberg and Irving L. Rosen, New Orleans, La.

A schema has been devised which makes it possible to express the relation to cycle length of the repolarization potentials of the human heart in terms of the physiologic unit, the monophasic action potential curve (MAP). Adhering to the classical theory of Lewis, Wilson, Ashman, and Bayley, variation in the rate of repolarization in the human heart is represented in the simplest possible manner. This involves the construction of a curve for each of 2 areas whose rates of repolarization differ. Each curve represents the relation of the duration of the MAP to cycle length. The vertical distance between the curves at any cycle length is proportional to the magnitude of the ventricular gradient at that cycle length. The schema is found to correlate well with the available data relating the magnitude of the ventricular gradient to cycle length and a variety of clinical phenomena in the normal and in the presence of ischemia.

The reversal of the direction of the inverted T wave with rapid rate in the presence of ischemia, and its reinversion with further increase in rate, is furnished with a sound physiologic basis. The same physiologic basis is shown to hold for variations in this phenomenon as well as for variations in the effect of abrupt change in cycle length due to carotid sinus stimulation.

Employment of the schema brings order to a variety of clinically important electrocardiographic phenomena and exposes a number of areas, hitherto neglected, that require investigation.

Present Status of the Electrocardiographic and Vectorcardiographic Diagnosis of Right Ventricular Hypertrophy

Manuel Gardberg and Irving L. Rosen, New Orleans, La.

Close examination of all of the reliable empirical and experimental evidence available as well as theoretic analysis were combined to study the value and limitations of the conventional electrocardiogram and 2 methods of vectorcardiography (cube and Frank) when they are applied to the diagnosis of right ventricular hypertrophy. Young infants constitute the only large group of individuals in whom the right ventricle is relatively hypertrophied, and regarding whom reliable anatomic data is available. Therefore, serial electrocardiographic observations made on young infants were employed as the initial approach to an empiric and a theoretic analysis.

The accumulated evidence indicates that the conventional electrocardiogram (limb leads and right precordial leads), the cube vectorcardiogram and the Frank vectorcardiogram all exaggerate the right ventricular effects in the presence of right ventricular hypertrophy. This phenomenon results from the errors resulting from eccentricity and from the assumption of the validity of single dipole representation under the conditions of right ventricular hypertrophy.

For normal young infants, these errors of the conventional leads and of the cube vectorcardiogram are sufficiently parallel so that it is possible to predict the horizontal loop of the cube from the form of the conventional leads, both when the right ventricle is relatively thicker than in the normal adult (first 3 months) and after the more adult relations have been attained.

When electrocardiograms and vectorcardiograms from cases of right ventricular hypertrophy result

ing from congenital heart disease are examined, essentially the same correlations are observed that were noted in normal infants. Furthermore, when it is difficult to recognize right ventricular hypertrophy in the electrocardiogram, it is usually difficult to recognize it in the vectorcardiogram. Only in rare cases is it possible to entertain the suggestion that portrayal of the phase relationship of 2 leads in the vectorcardiogram may be valuable in the diagnosis of right ventricular hypertrophy, but this matter must be examined more carefully than has hitherto been done.

Those cases in which the presence of right bundle-branch block and right bundle-branch delay must be considered have been examined by comparing the path of excitation in right bundle-branch block (verified by Scher) with that which is hypothetically believed to obtain in right ventricular hypertrophy. It is hardly possible to avoid the conclusion that when difficulty in distinguishing the 2 conditions arises in the conventional leads, it is equally present in the vectorcardiogram. The basis for distinction that has been employed is illogical. The problem is further complicated by the not infrequent presence of both right ventricular hypertrophy and right bundle-branch delay in the same heart.

Further Observations of the Natural Course of Ventricular Septal Defects: New Clinical and Physiologic Data

Benjamin M. Gasul, Robert F. Dillon, and Vlastimil Vrla, Chicago, Ill.

During the past 10 years we have studied 346 patients with ventricular septal defects. Ninety-five of them had cardiac catheterization and 90 had angiocardiographic studies; 6 had surgical intervention. The natural course of patients with these defects is not definitely known. There were 28 autopsies performed on these patients. Twenty-six of them were under 6 months of age, and one was 14 months old. We have found that a number of these patients who previously had a loud, booming second sound over the pulmonary area as a sign of high pressure in the lesser circulation presented, on subsequent re-examinations, a definitely diminished second sound over this area. We then decided to recatheterize some of these patients, especially those who had had cardiac catheterization performed in infancy several years previously. So far we have recatheterized 15 patients with ventricular septal defects. Eight of them had their initial catheterization before the age of 1 year, and the other 7 before the age of 6. The interval between catheterizations varied from 2 to 4 years.

We have documented for the first time that some patients with ventricular septal defects were naturally transformed into what has been hitherto considered separate entities. There was a natural transformation of patients with ventricular septal defects into ventricular septal defects with infundibular stenosis and marked gradient between the right ventricle and pulmonary artery of 45 and 70 mm. Hg in 2 patients, and with a mild insignificant gradient of 14 and 18 mm. Hg in another 2 patients. There was a natural transformation into tetralogy of Fallot with peripheral arterial oxygen unsaturation of 74 and 86 per cent in another 2 patients. Two patients presented persistent marked pulmonary hypertension, and a third patient developed arterial unsaturation of 85 per cent with a persistence of severe pulmonary hypertension. Six patients showed a regression from moderate or mild right ventricular hypertension (60 and 45 mm. Hg) to normal pressures.

Treatment of Acute Myocardial Infarction in Man with Cortisone

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In previous publications we reported on the use of cortisone in experimentally produced acute myocardial infarction in dogs, which revealed the following: (1) increased vascularity of the myocardium, (2) decreased mortality rate, (3) a smaller area of residual fibrosis, (4) fewer thromboses in the smaller vessels, and (5) a speedier recovery from a general anesthetic than the control animals. We felt that these findings indicated that the primary action of cortisone was vascular (coronary and cerebral vasodilatation and peripheral vasoconstriction). After review by the Research Committees of the Michigan Heart Association and Harper Hospital the following clinical study was undertaken. Thirty-eight cases of acute myocardial infarction were studied. Twenty-eight were treated with intramuscular cortisone for 10 days. Both treated and untreated patients usually revealed a drop in total circulating eosinophiles, sedimentation rate and white blood count elevations, and a transient rise in fasting blood sugar. Twenty-five per cent (7 of 28) of the treated group died. In those also treated with Dicumarol, the Dicumarol requirement was slightly greater after cortisone was discontinued. Eight had some form of arrhythmia. Nineteen cases had associated shock and congestive failure. The mental attitude toward their illness was very good. There were no untoward effects attributable to the cortisone therapy. Congestive failure was treated with the usual measures. This is a relatively small group studied and no definite conclusions can be drawn. A considerable amount of detailed information, however, has been recorded. The authors feel that both experimental and clinical evidence indicated that cortisone may be of definite value in the treatment of acute myocardial infarction and further detailed clinical study should be continued.

Further Mechanism for Quinidine Action on Cardiac Muscle

Menard M. Gertler, New York, N. Y.

It has been established on clinical grounds that quinidine preparations are useful anti-arrhythmial agents. The mechanism of their action has been partially explained by such physiologic properties as depression of conductivity, or influence on the refractory period of the myocardium.

In attempting to ascertain additional mechanisms of quinidine action, it was deemed advisable to study the shifts in intracellular electrolytes in cardiac muscle. The basis for this action stemmed from the well-established observations that digitalis preparations produce a depletion of intracellular cardiac potassium and alter other intracardiac electrolytes, and that quinidine is antagonistic to digitalis-produced cardiac arrhythmias.

Seventy-four male albino rabbits, weighing from 2,650–3,400 Gm., were divided into 4 groups (a) quinidine treated, (b) quinidine control, (c) digitalis treated, (d) digitalis control. Prior to treatment, serum electrolytes (sodium, potassium, chlorides) and nitrogen were determined in all animals. After a suitable period to establish and maintain digitalis effect or quinidine effect, the animals were sacrificed. Serum determinations for the above electrolytes and nitrogen were repeated. The heart was removed immediately from each animal, as was an aliquot of gluteus maximus muscle. Electrolyte, water content and nitrogen were determined for each individual tissue and derived values, based on Hastings and Eichelberger's method, were made in order to evaluate the distribution in the intracellular and extracellular spaces.

It was observed that a gain of 16.0 mEq. of potassium and a loss of 6.8 mEq. of sodium per L. of intracellular water occurred in the hearts of the quinidine-treated animals. The significance of these findings, in terms of bio-energetics and enzyme control, will be discussed.

Hemodynamic Reactions to Endotoxin

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Experiments have been carried out with gram-negative bacterial endotoxin in an effort to elucidate the mechanism of bacteremic shock. The variability of vascular effects in different species does not yet allow a direct translation of these findings to patients.

The early vascular effects probably do not represent a direct action since blood components have been found necessary for endotoxin to act in 2 types of isolated preparation. These early effects are widespread and include the veins.

Studies in the dog, cat and monkey have shown an early, nonsustained rise in portal venous pressure. This is important in the dog where there is hepatic vein constriction, hepatic engorgement, a high portal pressure and a resultant drop in venous return sufficient to cause severe hypotension. After the portal pressure has returned to normal there is still progressive fluid volume gain by the gut. Splanchnic changes are minimal in the cat and monkey.

The pulmonary vascular resistance rises in all 3 species, but particularly in the cat where it is associated with an acute hypotension and frequently leads to pulmonary edema and death. Studies in the dog and cat have shown a pronounced increase in pulmonary venous resistance.

Experiments with perfused dog limbs at constant flow have shown an increase in resistance, a slight rise in the small vein pressure and a gain in weight.

After subsidence of the acute splanchnic effects in dogs and of the acute pulmonary effects in cats the blood pressure tends to recover before starting a final decline to severe hypotensive levels. In the monkey there is no acute pressure drop but only the steady fall over several hours before death. The relative importance of these various mechanisms in patients remains to be settled.

Indications for the Surgical Treatment of Mitral Stenosis During Pregnancy

Frank Glenn and Curtis L. Mendelson, New York, N. Y.

Cardiac disease is now the chief contributing cause to maternal deaths in pregnancy. Ninety per cent of cardiac disease in this group is rheumatic. Two thirds of the rheumatic cardiacs have a mitral stenosis as the predominating lesion. Pregnancy is accompanied by an increase in cardiac output and therefore an increased flow through the mitral valve. Since this cannot readily take place in mitral stenosis, the result is that the left atrial pressure increased and this backs up to increase the pulmonary capillary pressure. If this becomes great enough, pulmonary edema occurs. Thus, a patient with mitral stenosis may have minimal symptoms until she becomes pregnant, and then the combination of mitral disease and pregnancy may produce a situation leading to pulmonary edema and death. Few clinics have reported on their experience with mitral commissurotomy during pregnancy. Over a period of 5 years, 20 pregnant women with mitral stenosis who have developed severe disability (pulmonary edema) within the first 6 months of gestation have been subjected to mitral commissurotomy. There has been no maternal mortality. Gestation has terminated with normal delivery save in a few instances. The indications for operation and the experience with these 20 patients in summary form is included in the presentation.

Division of Internal Mammary Arteries as a Means of Enhancing Myocardial Circulation

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Recent reports by European workers, indicating that ligation of the internal mammary arteries has resulted in dramatic relief of angina, have aroused the authors' interest. Studies to ascertain the anatomic basis for these claims have been carried out. Tracer substances injected into the proximal segment of the internal mammary arteries after ligation at the second intercostal space have been recovered in the coronary sinus, indicating a substantial contribution to myocardial circulation from this extracardiac source. Bilateral ligation of the internal mammary arteries has been shown to afford a measure of myocardial protection in animals subjected to acute occlusion of the anterior descending coronary artery.

The initial clinical application of this surgical effort will be presented. Subjective evidence of improvement has been obtained in 68 per cent (34 of 50), and objective evidence in 42 per cent (21 of 50), of patients so treated to date.

Recurrent Mitral Stenosis

Harry Goldberg, Charles P. Bailey, and William Likoff, Philadelphia, Pa.

The re-establishment of mitral valve obstruction, after its initial relief by surgery, constitutes a recurrence of mitral stenosis. The difficulties and confusions attendant upon the diagnosis have caused the authors to include as recurrent mitral stenosis only those patients in whom the evidence was obtained at autopsy or at the time of reoperation.

The material of this study was obtained from a review of our first 1,000 patients operated on for mitral valve obstruction. In each instance, the left atrial appendage was the surgical portal to the valve.

Among those who survived commissurotomy, 9 patients were improved clinically for 1 to 3 years, and then developed congestive heart failure and died. In each a severe degree of mitral stenosis was found at autopsy, with extreme refusion of the commissures which had been separated previously.

In 29 patients, reoperation was carried out because of the return of symptoms similar to those originally associated with mitral stenosis. Prior to reoperation, left heart catheterization revealed the presence of an abnormal gradient between the left atrium and ventricle. At operation re-establishment of mitral valve obstruction was demonstrated and corrected.

In general it would seem that recurrent mitral stenosis arises independent of acute rheumatic activity. It may develop as a result of a continuation of a chronic rheumatic state, incomplete surgical mobilization of the valve at the initial operation, or a morphologic state precluding proper correction.

Cinefluorography of Heart and Lungs

Robert S. Green, Cincinnati, Ohio.

The dynamics of heart and lung action, of the barium swallow, and of angiocardiography, particularly during cardiac catheterization, were studied by means of cinefluorography in more than 100 normal subjects and patients with cardiovascular disease.

Three and three-quarters, 7, 15 and 30 fluoroscopic images per second were photographed on 35 mm. film. The area of the fluoroscopic screen photographed varied from 64 to 110 square inches. The speed of the x-ray exposure was $\frac{1}{30}$ or $\frac{1}{60}$ second for all film speeds. This allowed as many as 440 exposures during 14 seconds, or runs of more than 5 minutes at $3\frac{3}{4}$ frames per second. The camera was used in both the erect or horizontal positions.

The films demonstrated: 1. Varying degrees of hilar activity. 2. Various types of the cardiovascular imprint on the barium-filled esophagus. 3. Angiocardiograms of normal subjects and of defects in patients with congenital heart disease. The contrast substance was usually injected serially in each of several chambers, e.g., pulmonary artery, right ventricle, right atrium, etc. The dynamics of several defects, e.g., interatrial and interventricular septal, patent ductus arteriosus, were visualized.

This method of study has aided materially in the study of cardiovascular physiology and in the diagnosis of cardiovascular defects.

Patients received from less than 1 up to 16 Roentgens over the chest area during the various procedures. Personnel protection was adequate.

Experiences with Anterior Percutaneous Left Heart Puncture in Valvular Heart Disease

David G. Greene, John T. Sharp, Geraint T. Griffith, Ivan L. Bunnell, and Joseph E. Macmanus, Buffalo, N. Y.*

Left atrial puncture by the technic of Radner through the suprasternal notch combined with direct puncture of the left ventricle through the anterior chest wall provides a safe and simple method of obtaining pressure gradients across the mitral and aortic valves. This approach does not require fluoroscopy and is performed with the patient supine. We have combined this method with right heart catheterization and the measurement of blood flow by the direct Fick technic or by dye dilution methods. The information so obtained is often of critical importance in the selection of patients for surgery for mitral or aortic stenosis. It is easily combined with thoracotomy which may immediately follow. Pressures in the left atrium, left ventricle and aorta in the open chest may be used to measure the gradients also. The correlation between the two types of measurements is reasonable. The pressures in the open chest may be used as an indication of the success of the surgical maneuver.

Effect of Alteration of Coronary Perfusion Pressure on Oxygen Uptake of Left Myocardium

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Studies have been made of the effect of alteration of coronary perfusion pressure on the oxygen uptake of the left myocardium. In the open chest dog the left coronary artery was perfused with blood at body temperature under constant pressure and the flow quantitated by a rotameter. Flow through the coronary sinus was isolated by a polyvinyl tube, one end of which was tied into the coronary sinus and the other end joined to a plastic tube opening into the right atrium or the atmosphere. Coronary arteriovenous oxygen difference was recorded continuously by withdrawing aliquots of systemic arterial blood and coronary sinus blood through recording densitometers. The coronary perfusion pressure was abruptly or gradually altered by from 5 to 35 mm. Hg while recording continued.

When coronary perfusion pressure was increased, the apparent oxygen uptake of the left ventricle increased. This was maintained, and the excess of oxygen usually varied from 20 to 70 per cent of that taken up by the left ventricle before elevation of coronary perfusion pressure. The heart rate, cardiac output, aortic blood pressure, and left ventricular end diastolic pressure did not necessarily change. Similarly, when coronary perfusion pressure was decreased the oxygen uptake decreased.

Thus far, experimental attempts to relate this observation to an artefact have been unsuccessful and include the following possibilities: an increase in the hematocrit of the coronary sinus blood; a relative increase in the volume and oxygen content of the fraction of left coronary inflow not draining into the coronary sinus; flushing into the coronary sinus of blood more highly unsaturated than that in the coronary sinus; and forcing into the myocardium in increased amounts plasma substances which stimulated metabolism. The physiologic significance of this phenomenon remains to be determined.

High Sensitivity Pickup for Cardiovascular Sounds

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Cardiologists have long known that certain heart murmurs of low intensity, those which are often of the greatest importance in early diagnosis of valvular disease, may be audible on careful stethoscopic examination yet not recorded on the phonocardiogram. There has long been a need for a practicable electronic method of detecting and recording heart murmurs of very low intensity.

Accomplishing this necessitates a pickup having high sensitivity and wide range, and extremely low levels of ambient noise both in the recording system and in the environment. Such a pickup has been devised. It is of a basically different type, one not involving air conduction of sounds, and consists essentially of a capacitance transducer which can utilize the body surface itself as one electrode of the capacitor.

Application of this relatively simple device in a sound-proof room, enables one to record or to amplify for listening sounds which are at and below the threshold of stethoscopic audibility, including systolic murmurs present in a high percentage of fetal and presumably normal adult hearts. An interesting research application lies in its capability of recording sounds directly from the surface of the open heart without touching the surface.

Clinical and experimental tests of the capacitance pickup indicate that it is uniquely suited to the recording and study of cardiovascular sounds.

Coronary and Aortic Atherosclerosis: Comparative Incidence in the Negro Race in Haiti and the United States

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This is the report of a 2-year study of the incidence of atherosclerosis in a single race under 2 contrasting environments: that of the southeastern United States and the relatively primitive environment of Haiti. Basis of the comparative study is pathologic examination of actual autopsy material from the 2 countries. The hearts and aortas from 140 consecutive autopsies at the Medical Center Hospitals of the Medical College of South Carolina were compared with those of 122 from the Hospital Generale at Port-au-Prince, Haiti. Routine autopsies, covering many types of mortality of subjects over age 20, were utilized as samples of the 2 populations and appropriate clinical data were obtained on each case. All coronary arteries and aortas were systematically sectioned, examined grossly and microscopically, and graded as to degree of atherosclerosis on a scale of 0 to 4 by one pathologist, specimens from the 2 countries being examined together with their origin unknown to him. Compilation of data was in terms of age groups by decade, sex, rural or urban origin, and economic class.

Dietary surveys were likewise carried out in both population groups to determine the basic differences in food habits and nutrition. Average diets were calculated from several sources, chiefly observations in the homes of representative families where foods were weighed and cataloged as to protein, fat, and carbohydrate content, with special reference to types of fats, as well as total caloric intakes.

Although diet may well be the dominant factor it is recognized that other environmental differences do exist between the 2 countries which may be o

significance in atherosclerosis. Fundamentally this pathologic study concerns what the American way of life does to a race as regards coronary and aortic atherosclerosis.

Role of Electrolytes in Origin of Ischemic Cardiac Pain and Associated Electrocardiographic Abnormalities

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The effects of acute alterations of myocardial potassium on resting and postexercise electrocardiograms and on anginal pain were studied in 18 patients with coronary artery disease. Lowering of potassium was produced by infusion of 120 ml. of molar sodium lactate within a 5-minute period, and elevation of potassium was produced by infusion of 30 mEq. of KCl in 500 ml. 5 per cent glucose in water in a 25- to 30-minute period.

Sodium lactate produced electrocardiographic changes similar to those which developed on performance of a double two-step exercise test. In 5 patients attacks of anginal pain were induced by the sodium lactate infusion with accompanying S-T segmental depression. Ischemic electrocardiographic changes produced by exercise were augmented when the double two-step test was performed immediately after sodium lactate infusion. Conversely, when KCl was administered prior to exercise, S-T segment and T wave abnormalities were minimized or did not appear. Exercise tolerance was increased in patients with angina pectoris pretreated with KCl, and pain did not develop on exercise or was milder in degree than on control exercise tests. In 2 patients with acute myocardial infarction, 30 mEq. of KCl were given during the initial period of severe pain, and in both temporary relief occurred.

These observations indicate that the determining factor producing ischemic electrocardiographic changes and anginal pain is not anoxia per se, but an acute alteration in myocardial potassium produced by ischemia. Factors which tend to provoke anginal attacks in patients with coronary disease, such as stress, anoxia, tachycardia, cold, food (glucose-insulin), and digitalis, all share in common the effect of lowering myocardial and serum potassium.

Reversal of the Currents of Injury by Intracoronary Injections of Various Electrolytes

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It has been observed that in some cases of hyperpotassemia the RS-T segment of the electrocardiogram is elevated as it is in acute myocardial infarction and/or pericarditis. The studies to be presented show that these electrocardiographic "currents of injury" could consistently be produced by intracoronary arterial injections of potassium chloride, sodium cyanide, strophanthin and pitressin. This RS-T segment elevation could be reversed by intracoronary injections of various sodium salt solutions.

In anesthetized dogs with intact chests, the anterior descending branch of the left coronary artery was catheterized through one of the carotid arteries under fluoroscopic guidance. Continuous electrocardiograms (leads II, aV_R and V_3) and femoral arterial blood pressure were recorded.

Solutions of sodium chloride (0.85 per cent), sodium bicarbonate (7.5 per cent) and sodium lactate (1.87 per cent) when injected into the anterior descending branch of the left coronary artery resulted in lowering or inversion of the T wave, resembling an "ischemic" pattern. More profound changes consisting of S-T depression and deeper T wave inversion were observed when molar solutions of the same electrolytes (11.2 per cent sodium lactate, 8.4 per sent sodium bicarbonate and 5.8 per cent sodium chloride) were injected. Dextrose (5 per cent) in water and molar dextrose solution (18 per cent) had essentially no electrocardiographic effects when injected into the same site. All the above solutions injected were within the range of 0.2 to 0.5 ml.

Intracoronary injections of 1.15 per cent potassium chloride (0.2 to 0.5 ml.), sodium cyanide (0.08 mg. per Kg.), strophanthin (2 μ per Kg.), and pitressin (0.02 to 0.1 U. per Kg.) into the left anterior descending branch resulted in a marked elevation of the RS-T segment, similar to the electrocardiographic changes following acute coronary occlusion. These "currents of injury" were reversed following coronary arterial injections (same site) of the different sodium salts, previously enumerated, with the molar concentrations being more effective. The RS-T segment lowering was, however, transient and became elevated again within a minute following the electrolyte injections.

These findings of a rapid reversion of the elevated RS-T segment by electrolyte alteration, suggest that an ionic imbalance occurs as the initial (biochemical) phase following myocardial injury.

Mechanics of Breathing and Circulatory Changes in Patients with the Syndrome of Extreme Obesity, Polycythemia, Hypoventilation and Cor Pulmonale

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Ten patients with the syndrome of extreme obesity, polycythemia, hypoventilation and cor pulmonale were investigated to determine the mechanics of breathing and circulatory status in this condition.

Weights of the patients ranged from 250 to 460 pounds. The clinical picture included somnolence, dyspnea, Cheyne-Stokes respiration, ankle edema and cyanosis.

The studies included: lung volumes, 2-level oxygen studies (Riley's method) and pulmonary compliance and resistance (intraesophageal method). Intragastric pressures were studied in 5 patients; right heart catheterization was performed in 4 patients.

The results were as follows (mean values given): Increased arterial pCO_2 (66 mm. Hg), marked arterial hypoxemia (78 per cent saturation). Arterial pH ranged from 7.28 to 7.42. Whole blood volume increased (11.62 L.). Hematocrit elevated (60 per cent). Cardiac output normal or increased. Pulmonary artery pressures increased (74/30 mm. Hg). Vital capacity, especially the expiratory reserve volume, decreased; residual lung volume, normal or low. Pulmonary compliance decreased and resistance increased; diffusing capacity, normal or low. Work of breathing increased. Abdominal pressure (intragastric) increased (sitting, 16.2 cm. H_2O, supine 21.4 cm. H_2O).

Initial management of the congestive failure by digitalis, diuretics, and reducing diet usually resulted in an early weight loss. This in turn was associated with prompt improvement of the vital capacity, expiratory reserve volume, pulmonary compliance and resistance, arterial oxygen saturation, and arterial carbon dioxide tension. The pCO_2 decreased from 73 mm. Hg to 49 mm. Hg within 3 weeks in 3 patients. Further improvement occurred after additional weight loss and phlebotomies.

The findings indicate that the work of breathing was markedly reduced after treatment, even though the weight loss was not great. It is suggested that the increased work of breathing is the important cause of the hypoventilation which occurs in this condition.

Circulatory Effects of Hypothermia in the Hind Limb of the Dog

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Cold block or injury seems a more likely cause than anoxia for peripheral nerve dysfunction in the posthypothermic surgical patient. To study degree of peripheral cold injury, hypothermia was induced in 12 dogs. Observations of rectal, esophageal, and hind limb intramuscular (IM) temperatures by thermistors, femoral arterial (FA) flows (in 6), pulse and blood pressure, Na^{24} clearances (in 5), and femoral arteriovenous oxygen (in 2) were made.

IM extremity temperatures were lower than rectal and esophageal during prehypothermia, changed more precipitously than central temperatures during induction and rewarming, and were far lower with greater deviations at the stable period of hypothermia. Temperatures usually drifted again toward hypothermia during the post-rewarming phase. Mean values during hypothermia ranged from 25.9 to 30.8 C. rectally, 25.6 to 31.6 in the esophagus, and often ranged less than 20.0 in the extremities.

Direct FA volume flows (bubble flow meter method) were not consistently altered. However peripheral resistances, if altered, were increased during hypothermia. Tissue clearances of Na^{24} were reduced during hypothermia but were not always accompanied by a fall in blood pressures. While the more marked cooling of the extremities does not bear directly on the cause for peripheral nerve dysfunction in patients, it is compatible with the hypothesis that cold block or injury of nerves may result in this disorder. Secondary downward temperature drifts after hypothermia in dogs suggest circulatory or central nervous system temperature regulatory failure and point up the need for correlated total body circulatory studies, including cardiac output. Low clearance ratios, despite relatively unaltered volume blood flows, suggest the possibility of increased shunting of blood in the extremity during hypothermia.

Serum Cholesterol, Diet and Stress in Patients with Coronary Artery Disease

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Careful measurements of serum cholesterol were made each week for an average of 9, and up to 14, months in a group of 12 male subjects (ages 30 to 70) who had survived a well documented myocardial infarction. The method gave reproducibility in duplicate samples within 2 per cent and recoveries better than 98 per cent. Each subject kept a daily record of what he ate. The diets were relatively high in cholesterol and fat content and were maintained at the same level throughout the period of study. There were no significant changes in body weight and no gross changes in the amount of exercise performed. A strong and positive patient-physician relationship developed but no therapeutic agents were administered. Nevertheless, in every patient, a decrease in serum cholesterol was observed over the 9 months of the study. The mean decrease for the group was statistically significant ($p = 0.001$).

Independent of the chemical determinations, each patient was studied carefully from the standpoint of his life adjustment and his reaction to people and events in his day-by-day experiences, and judgements covering each week were recorded. In addition to the over-all downward trend of serum cholesterol, there were significant variations from week to week. The average intraindividual range was 103 mg. per cent. On 20 occasions serum cholesterol rose higher than the mean value for that individual by more than 15 per cent. It was striking that 19 of the 20 occasions of high cholesterol corresponded with periods that had been separately judged as particularly stressful for the individuals concerned.

Dynamics of Edema Formation and Reabsorption

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The dynamics of edema formation have been investigated in 10 patients with cardiac and renal disease. Radioactive serum albumin has been injected intravenously and serial venous blood samples have been taken during the following 2 weeks. For periods up to 9 days after injection, edema fluid has been collected by intermittent insertion of Southey tubes into the legs. The total protein in the serum and edema fluid has been determined and paper electrophoresis employed to estimate the amount of albumin present. The protein-bound radioactivity has been measured in the serum and edema fluid.

The concentration of albumin in edema fluid has ranged from 0.13 to 0.53 Gm. per 100 ml. and has increased during recovery from heart failure. The ratio of albumin to globulin has been higher in the edema fluid than in the blood, reflecting the greater permeability of the capillaries to the smaller albumin molecule.

The specific activity of albumin (radioactivity per milligram of albumin) has been calculated. The specific activity of the serum falls and that of the edema fluid rises, and they become equal after approximately 6 days. In most cases the rate of increase of specific activity in edema fluid is slower than its mean rate of disappearance from the blood. The magnitude of this discrepancy is dependent on the size of the extravascular protein reservoirs and the phase of edema formation or reabsorption. It appears, therefore, unlikely that increased capillary permeability in the legs is responsible for edema formation.

"Pseudostenosis" of the Aortic Valve

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In the course of 1 year, 7 patients, all men, ranging in age from 51 to 67 years, with good clinical evidence for aortic stenosis and significant cardiac symptoms were under serious consideration for aortic valvulotomy, but subsequently were shown to have no significant obstruction at the aortic valve. In 5 patients significant aortic stenosis was ruled out by percutaneous catheterization of the left heart which showed the absence of any measurable systolic pressure gradient across the aortic valve. In the 2 other patients postmortem examination demonstrated the absence of significant narrowing of the aortic valve orifice.

Clinically, each patient was thought to have essentially isolated aortic stenosis. All patients had symptoms of left ventricular failure, 3 had angina pectoris, 4 had syncope, and 2 had all 3 of these manifestations. Five had a murmur typical of aortic stenosis, associated with a thrill in 2; 6 had a diminished or absent aortic second sound; all showed radiologic evidence of left ventricular enlargement, and calcification of the aortic valve was demonstrable fluoroscopically in 5. The electrocardiographic evidence for left ventricular hypertrophy was definite in 4 and suggestive in 2 cases; 1 patient had a left bundle-branch block. The direct brachial arterial pressure pulse was normal in 4 and showed a prolonged systolic upstroke in 3.

Ultimately, in 5 cases, heart failure was attributed to coronary heart disease with myocardial fibrosis or infarction. In 2 cases catheterization of the left heart revealed mitral valvular disease not apparent clinically.

It is concluded that the clinical picture of aortic stenosis may be associated with a nonobstructing aortic valvular lesion in which case surgical treatment of the aortic valve is contraindicated. Catheterization of the left heart serves to avoid unnecessary operations in such patients.

Multiple Sounds in Paroxysmal Ventricular Tachycardia: An Aid in Diagnosis by Auscultation

W. Proctor Harvey and Michael A. Corrado, Washington, D. C.

The diagnosis of paroxysmal ventricular tachycardia by hearing multiple sounds may be more quickly suspected at the bedside. These are usually of low frequency and are best heard by listening specifically for them at the apex.

The auscultatory features of ventricular tachycardia well emphasized in the past are (a) a change in intensity of the first heart sound, (b) slightly irregular ventricular rate, and (c) failure of carotid sinus stimulation to slow the ventricular rate. In addition to these important auscultatory findings, the detection of multiple sounds leads one even more quickly to suspect the diagnosis.

Ventricular tachycardia usually sounds different on auscultation of the heart from other tachycardias. On more careful analysis it has become apparent that additional sounds play a major role in causing this auditory differentiation. The wide splitting of the first and second heart sounds, as with bundle-branch block, and gallop sounds combine to produce these auscultatory events.

Not every case of ventricular tachycardia will show these typical findings, but it is believed that the great majority will do so. It is predicted that the production of these sounds will be directly related to a number of factors, such as widening of the QRS complex, duration of ventricular tachycardia, lack of cardiac reserve, and degree of cardiac decompensation.

Clinical observations in all types of tachycardia

have been documented by phonocardiograms and illustrate the specificity of multiple sounds to ventricular tachycardia. Detection of these sounds in a patient with tachycardia has led to more prompt recognition and treatment.

Right-Sided Murmurs of Aortic Insufficiency

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On evaluation of a large group of patients with severe aortic insufficiency (approximately 400), a typical auscultatory finding was that of an early blowing diastolic murmur over the aortic area and generally best heard along the third left sternal border transmitting down to the apex. A few of the patients, however, have shown an atypical transmission in that the murmurs were of the loudest intensity along the right sternal border instead of the left. This has been an immediate clue that the patient falls into a group which is of unusual etiology producing the leak of the aortic valve. We have found this right-sided diastolic murmur in aneurysm of sinus of Valsalva, aortic dissection involving the first portion of the ascending aorta, lues, Marfan's syndrome with aortic medionecrosis, or a variant of a typical Marfan's but having aortic medionecrosis. The pathology producing the insufficiency has been in the region of the aortic ring, sinuses of Valsalva, or first portion of the ascending aorta, resulting in a rightward displacement of the aortic root. Such cases have been verified on x-ray and/or thoracic aortograms, operation, or at post mortem.

On the review of the literature concerning the significance of diastolic murmurs best transmitted along the right sternal border, its occurrence with luetic etiology has been noted. Otherwise there has been little reference to this finding.

Pulse Pressure and Left Ventricular Efficiency

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Available objective measurements of left ventricular efficiency require complex equipment and training. The response of the pulse pressure to a standard exercise shows promise of becoming an easily performed, reliable index of left ventricular function.

Starr has reported a close correlation between pulse pressure and left ventricular work in moving blood within the aorta. Seventy-six male individuals underwent an exercise based on age and weight over a 2-step apparatus. This followed a complete physical examination, a 12-lead electrocardiogram, and a 15-minute rest period. Blood pressure was recorded at rest, immediately, and at 1, 2, 4, 6, 8, and 10-minute intervals after exercise. Twenty subjects are included in the apparently normal group above 40 years of age, and 20 are in the normal group below 40 years of age. Eighteen patients comprise the group with a prior anterior myocardial infarction, and 18 comprise the group with a prior posterior infarction. Several indices including absolute rise in pulse pressure, rise in true work per beat, and per cent rise in true work and in pulse pressure above the resting level were determined. Per cent rise in pulse pressure was selected as the presently most convenient index.

Normal individuals above 40 years averaged a 57.4 per cent rise in pulse pressure. Those below 40 years averaged a 67.5 per cent rise. Patients with a prior posterior infarction averaged a 50.3 per cent rise, but those with an anterior infarction averaged only a 28.9 per cent rise. A lag in response (i.e., a greater pulse pressure at 1 or 2 minutes than immediately) occurred only once in the normal and 11 times in the abnormal group. If a less than 25 per cent rise in pulse pressure is arbitrarily selected as an abnormal response, only 1 of the 40 normals, 10 of the 18 anterior infarctions, and 3 of the 18 posterior infarctions, fell below this dividing percentile.

Electrocardiographic Syndrome of Short P-R Interval and Broad QRS Complexes: Clinical Study of 80 Cases

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An analysis has been made of the clinical records and electrocardiograms of 80 patients with the Wilson-Wolff-Parkinson-White syndrome studied in the University of Texas Medical Branch. This represents the largest reported series of this disorder. Incidence of the syndrome was 1.5 per 1,000 patients. The age of patients varied from 9 months to 82 years, and 60 per cent were males. Only 8 per cent were Negro, a low incidence in this race not having been previously stressed. Of the 32 patients with organic heart disease, most had coronary or hypertensive heart disease, but 6 had congenital cardiac abnormalities. There was a high incidence of psychiatric diagnoses (26 per cent), and 7 patients were followed during electroshock and deep insulin therapy. Forty-five patients (56 per cent) had arrhythmias, and there were observed 29 with atrial tachycardia, 6 with atrial fibrillation, and 2 with atrial flutter. In 14 patients, the arrhythmias complicated organic heart disease. Onset of recurrent atrial arrhythmias was rare over the age of 30 years. Broad QRS complexes during the arrhythmias were more frequent than previously reported, and simulated ventricular tachycardia and fibrillation. Two older patients died suddenly, presumably as a result of a mechanism disorder. Illustrative cases demonstrate how the WWPW configuration obscures the usual signs of myocardial infarction, and how it may lead to a false positive exercise tolerance test. The methods of termination and prevention of arrhythmias are summarized. Pronestyl seemed to be the most effective drug for termination of atrial arrhythmias not responding to vagal stimulation.

Effects of Hypoxia on Coronary Blood Flow and Myocardial Metabolism in Normal Human Subjects

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Coronary blood flow by the N_2O method and cardiac output by the direct Fick method were determined in 19 normal individuals at rest and during acute hypoxemia induced with 10 per cent oxygen. Coronary flow and cardiac work were correlated with the myocardial metabolism of O_2, CO_2, glucose, lactate and pyruvate. The conditions of the study caused a fall in arterial O_2 saturation to levels of 42 to 83 per cent but did not produce significant changes in the electrocardiogram.

The cardiac index increased from 3.6 ± 0.17 to 4.8 ± 0.38 L. per minute per M.², accompanied by a fall in mean brachial artery pressure from 92 ± 2.6 to 77 ± 4.0 mm. Hg. Therefore, total peripheral resistance decreased during hypoxia from 1305 ± 24.1 to 869 ± 70.0 dynes per second cm.$^{-5}$ Total left ventricular work increased from 8.1 ± 0.40 to 9.0 ± 1.11 Kg. M. per minute, but this change was not significant for the group.

Coronary blood flow increased from 81 ± 2.4 at rest to 150 ± 9.1 ml. per 100 Gm. per minute during hypoxia. There was an inverse correlation between arterial-coronary sinus difference of oxygen and coronary blood flow. This is expressed as a negative logarithmic curvilinear regression ($r = -0.47$, $p < 0.02$). As would be anticipated from this correlation, the myocardial O_2 consumption remained constant throughout the studies, with a mean at rest of 9.0 ± 0.28 ml. per 100 Gm. per minute and during hypoxia of 9.0 ± 0.63 ml. per 100 Gm. per minute. Coronary vascular resistance decreased from a mean control value of 1.16 ± 0.04 to 0.60 ± 0.06 mm. Hg per ml. per 100 Gm. per minute.

Significant increases occurred in arterial and coronary sinus levels of glucose, lactate and pyruvate during hypoxia, but no significant change in quantitative extraction of these substances was observed.

While pooled data suggest that the normal heart became more efficient during hypoxia, great individual variability was noted. There was no correlation between coronary flow and cardiac work, arterial pressure or myocardial O_2 consumption.

It is concluded that the response of the normal human heart to acute hypoxia consists of coronary arterial dilatation with an associated increase in coronary blood flow sufficient to maintain left ventricular oxygen consumption at normal levels.

Influence of Abnormal Plasma Proteins on the Clotting Mechanism

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A new theory of interference with the clotting mechanism is advanced, based on the observation that unusual plasma globulins complex with and coprecipitate clotting factors. This reduces or inactivates the clotting factors, resulting in hemorrhagic disorders. Such circulating complexes induce an unstable clotting mechanism, also causing an increased tendency to clot. This theory offers a reasonable explanation for the bleeding diatheses which occur in macroglobulinemia, cryoglobulinemia, multiple myeloma, liver damage, and uremia and for the less frequent simultaneous thrombotic tendency present in some of these disorders. It may also explain some instances of coronary occlusion.

In the present report the unusual protein was a euglobulin. The clotting factors complexed and bound by the euglobulin were prothrombin, factor V and total accelerator activities factors.

Three case studies are presented: 2 of macroglobulinemia and 1 of myocardial and splenic infarction. A dual hemorrhagic-thrombotic diathesis was present in the case of myocardial infarction (case 3) and in one of the cases of macroglobulinemia (case 1). A hemorrhagic diathesis alone was present in the second case of macroglobulinemia (case 2).

Precipitation of the euglobulin reduced certain plasma clotting factors, and these were identified in the euglobulin solutions. In case 1, prothrombin and total accelerator activities were studied. In case 2, euglobulin precipitation reduced the plasma prothrombin, total accelerator activity, factor V and, to a lesser extent, factor VII. Except for factor VII these were demonstrable in the euglobulin solution. In case 3, a euglobulin factor V complex was demonstrable which contained a minimum of 200 to 400 per cent of factor V activity. The normal factor V level of the native plasma was not affected by the precipitation of the euglobulin, hence the plasma contained a minimum of 300 to 500 per cent of factor V. These data prove the existence of intravascular complexing of factor V with euglobulin.

Electrolyte and Water Metabolism in Essential, Renal, and Steroid-Induced Hypertension

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In 25 subjects with essential hypertension and 15 with renal hypertension (bilateral kidney disease) exchangeable body sodium, potassium, and extracellular fluid volume were not significantly different from the values obtained in 25 normotensive controls and did not change following antihypertensive drug treatment or splanchnicectomy. However, in 4 subjects with hypertension caused by unilateral

kidney disease and in 7 with malignant hypertension, body sodium and extracellular fluid volume were elevated.

In 4 of 5 hypertensive patients with Cushing's disease and in 2 of 4 with primary hyperaldosteronism, 1 of whom had been previously splanchnicectomized, body sodium and extracellular fluid volume were normal. Body potassium, however, was markedly reduced in all 9 of the subjects. Repletion of body potassium to normal by dietary treatment was not accompanied by reduction in blood pressure. However, reduction in blood pressure to normal by adrenal surgery was associated with decreases in body sodium and extracellular fluid volume and increases in body potassium.

When desoxycorticosterone acetate or 9-α-fluorohydrocortisone was administered chronically, definite elevations in blood pressure occurred in 4 of 8 normal, and in all of 5 hypertensive, subjects, 2 of whom had previously been splanchnicectomized. Furthermore, in 5 hypertensive patients, these steroids abolished the therapeutic hypotensive effects of ganglionic blocking drugs. Increases in blood pressure after steroid therapy were not necessarily accompanied by edema or gain in weight but were associated with definite increases in body sodium and extracellular fluid volume and significant decreases in body potassium.

In conclusion, essential hypertension, unlike "steroid hypertension" is characterized by normal body fluid and electrolyte composition. Hypertension induced by steroids appears not to be mediated through the sympathetic nervous system but to be dependent on changes in body fluids and electrolytes. In malignant hypertension and hypertension caused by unilateral kidney disease, body sodium and extracellular fluid volume are elevated.

On Computing Cardiac Work

Carl R. Honig, Rochester, N. Y., and Stephen M. Tenney, Hanover, N. H.

Cardiac work varies with the phase relationships between pressure and volume and between mass and velocity, as well as with the magnitude of these variables. Evans' classical formula neglects the time course of ejection, and has therefore been adopted by those measuring mean flow by Fick or dye-dilution technics. Further potential errors have been introduced by ignoring kinetic work, by the widespread use of electric integration of peripheral pressure pulses, and, recently, by indirect estimates of both pressure and flow.

To evaluate the accuracy of standard estimates of work, instantaneous pressure and flow were simultaneously measured with a new strain gage flow meter situated just distal to the aortic valves. All measurements were made on normovolemic spontaneously breathing dogs, and were photographically recorded at paper speed 75 mm. per second. The product of pressure and flow rate at 0.01 second intervals throughout systole was plotted for representative beats before and after acute circulatory change. The area beneath such power-time curves was measured planimetrically, and represented true left ventricular pressure-volume work less that expended in the coronary circuit. Kinetic work was similarly obtained from instantaneous values of volume and linear velocity.

Mean aortic pressure over the cycle underestimates work by up to 35 per cent, particularly at low diastolic pressures; mean systolic pressure may be as much as 20 per cent too low. The error in neglecting the time course of ejection may be somewhat compensated for by the use of peripheral pressure pulses which usually exceed central aortic pressure in magnitude. True kinetic work is 2 to 6 times greater than indicated by mean data and may not be neglected. An experiment in which true work increased, whereas mean data indicated a decrease, will be presented in detail to illustrate how incorrect measurement of work may lead to serious misinterpretation of physiologic mechanisms.

Further Effects of Hydralazine in Hypertensive Patients Under Prior Successful Treatment with Ganglionic Blocking Agents

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In order to investigate the effect of hydralazine on the recumbent blood pressure in severely hypertensive patients whose standing blood pressures were under good control, 14 patients were started on hydralazine 100 mg. 4 times daily in addition to chlorisondamine or mecamylamine. This dose was maintained during a 6-month period in which the study was made. L.E. cell test, white blood cell count, sedimentation rate, cephalin flocculation, protein fractionation, and serum cholesterol, were performed routinely every 3 months on each patient. Because of severe headaches and/or edema, 6 patients had to discontinue hydralizine treatment. No cases of hydralazine disease have yet developed.

The home standing and lying systolic and diastolic blood pressures of the remaining 9 patients were recorded twice a day during at least 2 weeks before treatment, and during the whole period of study. When the hydralazine was added, 5 patients had a reduction (20 to 60 mm. Hg systolic and 5 to 30 mm. Hg diastolic) in the recumbent blood pressure only; 2 experienced a drop in both standing and lying blood pressure and had to reduce the dose of the ganglionic blocking agent; no beneficial effects were found in the remaining 2 patients. Addition of a placebo to the ganglionic blocking agent was used in 6 patients to control the study. No similar improvement was noted.

It is concluded that within the time interval and dose range of this study, addition of hydralazine to ganglionic blocking agents provides a more satis-

factory control of the blood pressure in the severely hypertensive patient.

Relation of Chemical Changes in the Blood to Control of Cardiac Output in Congestive Failure

William E. Huckabee, Boston, Mass.*

Failure of changes in cardiac output during activity (△C.O.) to be correlated with cardiac filling pressure in human subjects had led to the suggestion that filling is not an essential factor controlling C.O. If this is true, neither central venous pressure nor its relationship to △C.O. in patients would be an indication of degree of myocardial failure. The actual factors controlling human cardiac output are not known, however, present investigations of possible chemical control of the human circulation have yielded a high correlation with △C.O., analogous to the control of ventilation.

Twenty normal subjects and 26 patients with heart failure of severity from class II to IV were mildly exercised. Increases in cardiac index or stroke volume (△C.O.) in either group showed no correlation with changes in O_2 consumption, or in oxygen content or tension, pCO_2, pH, K^+, lactate, pyruvate, ketoglutarate, citrate, or glucose concentrations of mixed venous blood. Blood epinephrine concentrations fell, usually to zero. However, from these chemical data it was possible to calculate tissue anaerobic metabolic rate (rate of energy derivation from LDH system in substitution for oxygen). This rate showed a close correlation with △C.O. both in normals and also, quite surprisingly, in the very variable cardiac group. Slopes, however, were 79 ml. per minute of C.O. per ml. per minute, AMR in normals, and significantly lower in all the cardiacs (9 ml. per minute per ml. per minute), despite a similar average △C.O. Normals showed a significant intercept of 2074 ml. per minute, interpreted to be a "superimposed" △C.O. due to some other controlling factor (i.e., pressure). This factor was completely inapparent in the cardiac patients. All the failing hearts exhibited the same response curve, which was not affected by therapy and clinical improvement. Thus the patients appeared to differ widely in clinical severity only because of different peripheral phenomena and not because of myocardial differences. This myocardial response characteristic of human patients in failure is consistent with the concept of a permanent abnormality, as in myosin structural change.

First Heart Sound in Mitral Stenosis

Herbert N. Hultgren and Thomas F. Leo, San Francisco, Calif

Phonocardiographic studies of 40 patients with mitral stenosis have afforded an opportunity to investigate several significant features of the first heart sound in this disease. Twenty patients had surgically demonstrated tight stenosis with minimal regurgitation while 20 patients had stenosis with associated significant mitral regurgitation.

The sound of tricuspid closure was identified in 16 of 20 patients with tight stenosis and in 18 of 20 patients with combined lesions. The sound is usually inaudible, but it may be loud after short diastoles when it can be heard as the first component of a split first sound near the sternal margin. When the ventricular rhythm is irregular, graphic analysis of tricuspid sound intensity and the R-R interval demonstrates an inverse relationship, the sound being loudest when ventricular systole begins from .08 to 0.28 second after the preceding second sound. It occurs from .04 to .08 second after the QRS onset and coincides with the onset of pressure rise in the right ventricle and the initial .04 second of the apex impulse. Q-1st sound intervals may be erroneously short if measurements are made to the onset of the first sound instead of to the peak of the mitral component since the initial vibrations may be due to tricuspid closure.

The sound of mitral valve closure was identified in all 40 patients in the series. Contrary to other observers, the sound was equally delayed in patients with tight stenosis and in those with combined lesions. The sound was loud in 19 patients with tight stenosis and in 12 patients with combined lesions. In agreement with previous observations of Rytand, the sound of mitral valve closure demonstrated no consistent variation of intensity in patients with tight mitral stenosis who had atrial fibrillation. In 2 of 13 patients with combined lesions, however, the sound varied predictably in intensity, being loudest after short diastoles.

Occurrence of Hypertensive Toxemia in Mother-Daughter Pairs

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Hypertensive cardiovascular disease has long been considered to have a definite familial tendency. Much less is known of the hereditary nature of hypertensive toxemia of pregnancy. Several isolated reports refer to the occurrence of toxemia in sisters. In the present study, the maternal history of 100 toxemic patients is compared with the maternal history of 85 patients whose pregnancies were normal. All probands (the daughters) were born at The Johns Hopkins Hospital. These same patients were delivered of babies at The Johns Hopkins Hospital during the period between 1945 and 1954. Of the toxemic patients, 28 (28 per cent) were themselves born of toxemic pregnancies. Only 8 (9.4 per cent), a significantly smaller number ($p = 0.001$), of the control group were born of such pregnancies. However, approximately equal numbers (14 and 16) of the mothers of the patients in both groups experienced hypertensive toxemia during other pregnan-

cies. A 10-year follow-up of the mothers of each group shows that 25 of 54 (46.3 per cent) of the toxemic group had developed hypertension, whereas only 17 of 54 (31.5 per cent) of the mothers of the control group had developed hypertension. A smaller group on which a 20-year follow-up is available indicates a similar preponderance of hypertension in the mothers of the toxemic patients. However, the 10-year follow-up of only those mothers who had toxemia reveals the development of hypertension to an equal degree in the 2 groups. It is concluded that hypertensive toxemia of pregnancy displaces familial aggregation which is one expression of the familial, presumably inherited, tendency toward hypertensive disorders in general.

Hemodynamics and Myocardial Oxygen Consumption in Decompensated Portal Cirrhosis

John H. Huston and Thomas C. Puchner, Milwaukee, Wis.

Ten patients, known to have hepatic insufficiency due to far advanced portal cirrhosis, were studied by cardiac catheterization. All had marked laboratory evidence of hepatic insufficiency and 6 showed cerebral depression at the time of study. Preparation included abdominal paracentesis when clinical ascites was present. The control group consisted of normal subjects with a similar age and sex distribution. Cardiac output was determined by the Fick principle and coronary blood flow by the nitrous oxide saturation method.

The right atrial pressure, pulmonary artery pressure, systemic artery pressure, heart rate, arterial oxygen saturation, arteriovenous oxygen difference, and coronary sinus blood oxygen content values were all within their respective normal ranges and differences between the 2 groups were insignificant. Arterial oxygen content and arteriocoronary sinus blood oxygen difference values were 1.5 volume per cent lower in the cirrhotic group and reflected the hemoglobin deficit of 2 Gm. per cent as compared with the normal subjects.

In patients with far advanced portal cirrhosis, the oxygen consumption index was found to be 99 cc. per minute per M.^{2} (normal, 137 cc.) and the cardiac index was 2.4 L. per minute per M.^{2} (normal 3.5 L.). The systemic resistance index was 960 dynes per cm.$^{-5}$ per second per M.^{2} (normal, 683 dynes) and the left ventricular work index was 3.1 Kg. per M.^{2} (normal, 4.6 Kg. per M.^{2}). Coronary blood flow was 48 ml. per minute per 100 Gm. myocardium (normal, 73 ml. per minute) and the myocardial oxygen consumption was found to be 5.4 cc. per minute per 100 Gm. myocardium (normal, 9.0 cc. per minute). Coronary vascular resistance was 2.0 units (normals, 1.4 units). These differences are all of the magnitude of 30 to 40 per cent ($p = 0.02$) in each instance.

The usual hemodynamic pattern in portal cirrhosis is one of high cardiac output and low vascular resistance. Our patients presented a reversal of this pattern. We believe our findings show that in portal cirrhosis which has progressed to hepatic insufficiency: (1) a depression in oxygen metabolism of the total body including the heart occurs and is associated with a decreased cardiac output and myocardial blood flow; and (2) a comparable increase in peripheral vascular resistance develops.

These hemodynamic changes explain the interesting clinical observation of a prolonged circulation time and the disappearance of palmar erythema and spider hemangiomata in the end stages of portal cirrhosis.

Postpericardiotomy Syndrome Following Surgery of Nonrheumatic Heart Disease

Tomiko Ito, Mary Allen Engle, and Henry I. Goldberg, New York, N. Y.

A syndrome indistinguishable from the "postcommissurotomy syndrome" has been observed to occur among patients with congenital malformations of the heart who survived intrapericardial surgery. It appeared as frequently (12 of 22 pericardiotomies) as has been reported in rheumatic patients who recovered from mitral valve surgery (10 to 40 per cent). The syndrome developed following transventricular and transarterial valvoplasty for pulmonary stenosis, closure of septal defects, and exploration of the pericardium for inoperable congenital cardiac lesions. The feature common to these operations was wide incision of the pericardium. This postoperative complication was not noted after other operations for congenital heart disease wherein the pericardium was not disturbed, nor was it found in patients where a small segment of pericardium was clamped to permit the removal of a pericardial cyst. The characteristic findings of this group of nonrheumatic patients will be presented and illustrated by selected case reports.

Since the condition appeared after pericardial incision, with or without cardiotomy or valvotomy, the term "postpericardiotomy syndrome" is suggested as more universally applicable for this postoperative complication.

The syndrome is interpreted as a traumatic pericarditis, probably a reaction to blood in the pericardial sac. The occurrence of this postoperative manifestation in nonrheumatic subjects is a compelling argument against the concept that the syndrome in patients with mitral valvotomy represents reactivation of rheumatic fever.

Effect of Kidney-Derived Vasodilator, Tubulin, on Pressor Response to Desoxycorticosterone Acetate and Salt in Essential Hypertension

Benjamin Jablons, New York, N. Y., and Teresita T. Estrellado, Manila, Philippines.

Desoxycorticosterone acetate (DOCA), plus sodium chloride has been shown to produce an early

increased pressor response in certain cases of essential hypertension. A kidney-derived vasodilator, isolated by the senior author, has been shown to counteract the pressor effect of various agents both renal and extrarenal such as renin, hypertensin, epinephrine and norepinephrine.

This report deals with the effect of this kidney-derived vasodilator (tubulin) on the pressor influence of DOCA plus salt in 7 cases of uncomplicated essential hypertension. The 7 subjects were under hospital control from 6 months to several years. They were on low-salt diets during this period. All antihypertensive medication was suspended 14 days prior to the study, and the subject's blood pressure was recorded daily during this control period. After the 14-day control period, the subjects were placed on a regime of 5.0 mg. DOCA administered intramuscularly daily and were given a daily dose of 5 Gm. of salt. This regime lasted a total of 10 days. After the first 5 days, each subject was given 1 daily dose of 3.00 ml. tubulin intramuscularly for the subsequent 5 days. At the end of the 10-day period, the patients returned to the low-salt diet of the control period and were observed for 1 week.

In all cases the blood pressure increased during the first 5-day period with an increase ranging from 22 to 70 mm. Hg systolic and 0 to 30 mm. Hg diastolic above control levels. In 5 cases the blood pressure decreased below control levels during the second 5-day period with the administration of tubulin, an average of 20 mm. systolic and 9 to 10 mm. diastolic. In 2 cases the blood pressure decreased an average of 40 mm. during the second 5-day period, but did not fall below or to the control levels.

Subjective symptoms such as headache that appeared during the first 5-day period were completely relieved during the second 5-day period. These results indicate that tubulin can counteract the pressor influence of this extrarenal adrenal-derived steroid.

Effect of Kidney-Derived Vasodilator, Tubulin, on the Cardiovascular Response to Epinephrine and Norepinephrine

Benjamin Jablons, New York, N. Y., and Teresita T. Estrellado, Manila, Philippines.

The antiadrenergic effect of a kidney-derived vasodilator (tubulin) was studied in 21 subjects hospitalized for various conditions not related to hypertension.

Fifteen subjects were initially infused with 0.3 ml. of epinephrine in 500 ml. 5 per cent glucose solution administered at a constant rate of 5 γ per minute. Six subjects were infused with norepinephrine (4.0 mg. norepinephrine base) in 500 ml. 5 per cent glucose solution for a period of 60 minutes. Blood pressure and pulse rates were determined and subjective symptoms recorded at 5-minute intervals prior to, during, and after the infusion.

The following day the same infusions were repeated, however, 3.0 ml. tubulin was given 20 minutes prior to the infusion of epinephrine in 6 subjects (intramuscularly in opposite arm) and simultaneously in 9 subjects (intravenously in the opposite arm). Of the subjects infused with norepinephrine, 4 received prior administration of tubulin and 2 simultaneous administration.

All subjects reported that the symptoms such as palpitation, precordial pain, nausea, etc., which they experienced with the initial infusion were completely absent during the second infusion. Only 1 patient reported a slight feeling of weakness during this second infusion.

The hypertensive effect of the epinephrine resulted in increases in the systolic pressures from 7 to 24 mm. Hg (average 15) and diastolic pressures from 0 to 22 mm. (average 10) above normal control levels. This hypertensive effect was reduced by the presence of tubulin, an average of 8 mm. systolic and 5 mm. diastolic below normal control levels during the second infusion. The hypertensive effect of the norepinephrine was more pronounced with increases of 50 to 120 mm. systolic and 20 to 50 mm. diastolic. The second infusion showed average increases of only 20 mm. systolic and 15 mm. diastolic.

The pulse rate showed an average increase over control levels of 20 beats per minute with epinephrine alone and 30 beats per minute with norepinephrine alone. During the second infusion the pulse rate diminished an average of 5 beats per minute below normal control levels with epinephrine and tubulin, and 20 beats per minute with norepinephrine and tubulin.

It is noteworthy that the antiadrenergic effect of this kidney-derived vasodilator is not associated with an increase in heart rate.

Effect of Digitoxin on Potassium Transfer in the Frog Heart

Gerson Jacobs and Hettie Brenz, Philadelphia, Pa.

A promising theory of the action of digitalis upon heart muscle is that it affects the transfer kinetics of potassium by decreasing its rate of exchange. By means of a Hajdu frog heart cannula, the rate of influx of potassium was determined. One to 2 mg. of K^{42} were added to the upper reservoir and aliquots were periodically removed and measured in a well-counter. Circulation time within the closed system was 2 minutes, thus making 2-compartment analysis inaccurate. The half time of equilibration of K^{42} was not affected by aging of the preparation or by digitoxin. It appears that whatever effect digitalis has upon the frog heart's potassium metabolism, it is not upon its kinetics. These experiments do not support the theory of a direct action of digitalis upon potassium movement.

Blood Supply of the Human Sinoatrial Node

Thomas N. James and George E. Burch, New Orleans, La.

Knowledge of the blood supply of the human sinoatrial node is important for at least two reasons, to understand normal and abnormal cardiac conduction mechanisms and to anticipate problems confronting the cardiac surgeon.

This study was conducted with 43 fresh human hearts from patients dying of noncardiac causes. Casts were prepared by injection of vinylite into the coronary arteries and cardiac chambers, followed by corrosion with hydrochloric acid. This provided a spatially oriented replica of the heart.

The artery supplying the sinoatrial node was well demonstrated in 39 of the 43 hearts. This vessel arose from the right coronary artery in 24 (61 per cent) of the hearts, and from the left in 15 (39 per cent). Although it never arose from both coronary arteries in the same heart, communications with other atrial vessels did exist. After originating in the first few centimeters of the right or left coronary trunk, the course of this artery was cephalad and posterior to the anterior interatrial septal groove, whence it ascended until it was near the superior vena cava; there it terminated by encircling this great vein, sending branches over both atria and toward the inferior vena cava, in the region of the tail of the sinoatrial node.

Although isolated lesions of the artery to the sinoatrial node occur, it is more common to encounter lesions of this artery in association with disease of the main coronary trunks. Some of the arrhythmias associated with myocardial infarction are more easily understood when the blood supply of the human cardiac pacemaker is recalled.

During cardiac surgery, procedures which transgress the anterior interatrial septal groove can only on rare occasions be expected to avoid disturbing the main artery to the cardiac pacemaker.

Left Atrial Electrokymography in Mitral Insufficiency in Man: A Correlative Study by Angiocardiography, Left Heart Catheterization, and Experimental Production in Dogs

Richard D. Judge, Melvin M. Figley, and Herbert E. Sloan, Jr., Ann Arbor, Mich.

A better understanding of the origin of atrial border movements has resulted from a study of their relationship to underlying pressure and volume changes in patients with surgically proven mitral insufficiency and in dogs with experimentally produced mitral insufficiency. Observations in this study are divided into 4 sections: 1. The electrokymogram was correlated with left atrial volume changes as determined by angiocardiography. Volume variations plotted from serial films followed simple curves with minima at the onset of systole and maxima at the onset of diastole. With mitral insufficiency, the diastolic emptying pattern showed a rapid, early decrease in volume. This reflected the fact that the pressure gradient during this period was higher and there was no mechanical impedimen to flow. With mitral stenosis the emptying patter was different, showing only slight decrease in volum early in diastole. In all curves there was a strikin similarity between border movement curves an volume changes throughout ventricular diastole. 2 Correlation of the EKY with direct left atrial pres sure records in 11 cases showed a distinct similarity in form, particularly during ventricular systole. I appeared that border movements reflected varia tions in pressure except during atrial systole. 3 After creation of mitral insufficiency in 4 dogs, the form of the EKY changes to a pattern similar to that observed in clinical cases. The EKY pressure relationships were also similar. 4. On the basis of these observations, criteria for the recognition of hemodynamically significant mitral insufficiency by means of the EKY have been revised. Special emphasis is placed on a rapid inward movement of the atrial wall in early diastole. Applying these criteria to the interpretation of the EKY in 44 surgical patients (without additional clinical data) the correct lesion was predicted in 40.

Enhancement and Inhibition of Diuresis in Congestive Heart Failure

Stanley L. Kass, Jacob Grossman, Raymond E. Weston, and Louis Leiter, New York, N. Y.

The effects of acidifying and alkalinizing salts on mercurial diuresis have long been known, but the underlying mechanisms remain perplexing. Studies have implicated the electrolyte pattern, and presumably pH, of extracellular fluid, urinary pH, level of chloruresis, and other factors.

To dissect these diverse influences, the following diuretic studies were performed in patients under metabolic regimen, each subject serving as his own control. Carbonic anhydrase inhibition (acetazoleamide) was employed to create urinary alkalinity; repetition of the dose after 24 hours produced prompt urinary alkalinity associated with the previously established acidosis. Organic potassium salts (potassium triplex) were used to alkalinize body fluids and urine, potassium chloride to produce chloruresis without marked acidosis, and potassium acid phosphate (KH_2PO_4) to acidify urine without marked chloruresis or acidosis. Acetazoleamide and mercaptomerin were injected separately and together at varying intervals, and their effects on 2-, 6-, and 24-hour urinary water and electrolyte excretion measured.

Results. Preadministration of acetazoleamide greatly impaired mercurial response. Moreover when this combination was administered during acidosis produced by acetazoleamide given 24 hours

arlier, the impaired diuretic response suggested hat the inhibitory effect of urinary alkalinization revailed. Furthermore, acetazoleamide administration during mercurial diuresis promptly suppressed . While these data tend to attribute the magnitude f mercurial diuresis to urinary pH, they imply hereby a distal tubular effect inconsistent with ost previous studies. Changes in renal cellular pH, ather than urine, probably determine the response.

The use of potassium acid phosphate presented an xception to the accepted roles of alkalinization and cidification on acetazoleamide diuresis. This salt, hich acidifies urine and produces chloruresis interediate between that of organic potassium salts and otassium chloride, most enhanced acetazoleamide iuresis, suggesting that neither extracellular fluid or urinary alkalinity, nor a low urinary chloride xcretion is the primary stimulus; other factors must e sought.

Dynamics of the Coronary Collateral Flow in the Normal Open Chest Dog

Albert A. Kattus and Donald E. Gregg, Washington, D. C.

Although marked augmentation of coronary collateral circulation has been amply demonstrated in chronically ischemic hearts, little is known of the acute responses of the coronary arterial anastomotic pathways. The dynamics of the coronary collateral circulation have therefore been investigated in normal open chest dogs. Coronary collateral flow was measured by the retrograde flow technic in which the distal cut end of a proximally ligated left coronary artery branch is allowed to bleed to the outside. The fact that this retrograde flow is fully oxygenated gives evidence that it is conveyed to the occluded vessel through arterial anastomoses.

The amount of retrograde flow was studied in relation to the antegrade flow in the subsequently occluded vessel, the coronary perfusion pressure, the heart rate, the duration of occlusion, the hematocrit, the oxygen saturation of the perfusing blood, and the state of tension of the myocardium. The effect of coronary vasodilator drugs and reactive hyperemia was also investigated.

The data reveal a close positive correlation between the retrograde flow and the coronary perfusion pressure, but a poor correlation with the rate of inflow prior to occlusion of the vessel. Retrograde flow could not be augmented by reduction of heart rate, perfusing with blood of low oxygen saturation, perfusing with nitroglycerin, histamine or levophed, or by reducing the hematocrit provided viscosity was maintained with dextran.

Retrograde flow could be augmented by reducing the hematocrit with saline infusion, by reducing myocardial tension, or by increasing perfusion pressure. Retrograde flow was reduced during reactive hyperemia and by periods of occlusion lasting 1 to 8 minutes.

The findings suggest that the interarterial anastomotic blood vessels are small in caliber, that under normal conditions they are in a maximal state of dilatation, and that under some conditions of ischemia which dilate the arterial system these collateral channels are capable of constricting.

Coronary Flow and Oxygen Metabolism

Louis N. Katz, Harold Feinberg, and Augusto Gerola, Chicago, Ill.*

Evaluation of the relationship among coronary flow, myocardial oxygen metabolism, and cardiac activity has occupied the efforts of this laboratory for the past several years. This problem has been investigated in the open chest, anesthetized, but otherwise intact dog specially prepared for the measurement of total coronary flow. Our findings provide strong support for the concept that need for oxidative energy is the decisive factor determining coronary flow. This has been demonstrated experimentally under conditions of controlled variability in heart rate, cardiac output, and blood pressure respectively.

With changes in these 3 aspects of cardiovascular function, the arteriovenous oxygen difference was found to remain essentially constant over a wide range of oxygen consumption. Thus, increased need for oxygen was met *pari passu* by increased coronary flow. Under other experimental conditions, e.g., hypoxemia or catecholamine administration, A-V oxygen difference and oxygen extraction are altered. In the former condition decreased A-V oxygen difference was associated with an increase in coronary flow, thereby meeting myocardial oxygen need. When cardiac work was augmented in the hypoxic animal, increased myocardial oxygen need was met by concomitant increases in both coronary flow and oxygen extraction. In contrast, catecholamine administration was associated with an increase in coronary flow, a fall in A-V oxygen difference and in oxygen extraction. These findings emphasize the different dynamic interrelationship between myocardial oxidative-metabolic and hemodynamic functions in different experimental conditions.

Fibrinolysis Plus Circulating Anticoagulant During Heart Surgery with Pump-Oxygenator

Kurt von Kaulla and Henry Swan, Denver, Colo.*

A 17-year-old girl, operated on 2 years ago for patent ductus arteriosus and valvular pulmonic stenosis, underwent repair of an interventricular septal defect. Dissection of dense vascularized pleural and pericardial adhesions created a large raw area. An urticarial wheal and marked bleeding tendency developed during transfusion and after heparinization (3 mg. per Kg.). Potassium induced cardioplegia and bypass procedure lasted about 19 minutes. After restoration of heart beat, a persisting heart

block developed. Protamin (188 mg.) left oozing tendency unchanged. Platelets had dropped from 203,000 to 61,000, fibrinogen from 211 to 155 mg. per cent. More protamin (62 mg.) was without effect. Thirty-five minutes later platelets were 78,000, fibrinogen 74 mg. per cent, clot lysis time 15 minutes. Fibrinogen (11.2 Gm.) and extensive transfusions were given. One hour thereafter, coagulograms revealed normal recalcification time, but lysis started before completion of fibrin formation. Euglobulin lysis was 11 minutes (normal > 120 minutes), thrombin time 22 seconds (normal 7 seconds). Additional fibrinogen did not change severe anticoagulation and fibrinolysis. Sixty minutes later recalcification and thrombin time were indefinite, euglobulin lysis 4 minutes. If 3 ml. of patient's plasma were added to 7 ml. of normal plasma, the thrombin time was prolonged to 45 seconds, with lysis in 20 minutes; 4 ml. made it uncoagulable due to the high titer of anticoagulant. Additional fibrinogen (8 Gm.), 110 mg. protamin, 200 units ACTH and concentrated erythrocytes were given to the patient, and all values returned to normal in 2 hours. Throughout this period, blood pressure was maintained with difficulty at levels of 45 to 60 mm. Hg by rapid continuous transfusions. Patient received altogether 10 units of fresh heparinized, 4 of stored bank, and 7 of fresh citrated blood. The unavoidable prolonged manipulations with the lungs combined with allergic reaction, alterations of blood by the pump and possibly protamin might have induced release of plasminogen activator. Shock and/or proteolytic breakdown of heparin-protamin complex could have released heparin-like anticoagulant.

Surgical Treatment of Acquired Valvular Disease

Earle B. Kay, Frederick S. Cross, and Henry A. Zimmerman, Cleveland, Ohio.

Sufficient patients with cardiac anomalies of congenital origin have now been operated on by the open technic employing a pump-oxygenator to establish it. The application of this principle to the surgical treatment of acquired valvular lesions has been delayed because of the increased number of problems associated with left-sided cardiotomies. Among these factors were the necessity for larger oxygenators for use in adults, the technical aspects relative to the possibility of air embolism in left-sided cardiotomies, factors associated with elective cardiac arrest to prevent air embolism, development of surgical technics to be employed when operating on the aortic and mitral valves, and development of the proper pre- and postoperative management.

The need for better and more satisfactory surgical technics in the correction of aortic regurgitation and stenosis, and for mitral regurgitation, was most pressing in view of the failings inherent in the previous closed technics. As open heart surgery becomes further developed, it will undoubtedly also be applied to the treatment of mitral stenosis, for unquestionably such stenotic valves could be better opened under direct vision than by the blind or closed technics.

Nine patients with aortic or mitral valvular disease have now been operated upon. The conditions present were pure mitral regurgitation, the combination of mitral stenosis and regurgitation, aortic stenosis, combined aortic stenosis and regurgitation, and pure aortic regurgitation. The mitral valve has been exposed from both the left and right side. The right-sided approach appears to be the best. Pure mitral regurgitation has been corrected by decreasing the size of the annulus at the posteromedial commissure, the site of the regurgitant flow of blood. In the combination of mitral stenosis and regurgitation the commissures are first opened, following which the dilated annulus is reduced in size. In aortic stenosis the commissures are opened under direct vision and in aortic regurgitation the valve cusps are approximated by plicating the aortic annulus.

There has been an over-all mortality of 50 per cent in the early cases. The cause of death has been attributed to the early selection of very poor risk patients, myocardial failure, and difficulties associated with cardiac irregularities following arrest. Technics have now been developed in the research laboratory which allow us to operate upon the mitral valve without cardiac arrest and on the aortic valve with coronary artery perfusion while the aorta is open.

Clinical and Physiologic Manifestations of Tricuspid Stenosis

Thomas Killip III and Daniel S. Lukas, New York, N. Y.*

Tricuspid stenosis has been encountered in 12 of 260 patients with rheumatic heart disease studied by cardiac catheterization. It was isolated in 1, combined with mitral disease in 4 and with mitral and aortic lesions in 7. Two came to autopsy; 2 underwent tricuspid valvuloplasty.

In 11 a characteristic diastolic murmur and thrill in the left third, fourth, or fifth intercostal space established the diagnosis clinically. The tricuspid murmurs, in contrast to the mitral murmurs, increased during inspiration and decreased with expiration, thus permitting their differentiation. A significant fall in pressure from right atrium to ventricle during diastole was encountered in all at rest and increased during exercise. Variation in the gradient during the respiratory cycle paralleled the auscultatory changes. Cardiac output and pulmonary vascular pressures and resistance were lower than in similar patients who did not have tricuspid stenosis.

The degree of right atrial enlargement was varia

le but was massive in 5. Angiocardiograms in 6 demonstrated prolonged opacification of the right atrium and a sharp demarcation between atrium and ventricle in the plane of the tricuspid valve. The amplitude of the P wave was increased and contrasted with the frequently low QRS complexes. In 2, P was greater than QRS in V_1 or V_2.

Symptoms were variable. All suffered from dyspnea and most had orthopnea. Fatigue, best correlated with the low output, was common. Two had never had edema. Persistent ascites was encountered in only 2. The largest right atria, the greatest hepatomegaly, and most severe edema occurred in those who had multivalvular disease, tricuspid insufficiency as well as stenosis, atrial fibrillation and higher right atrial pressures.

Re-examination of the Mechanism of Arterial Hypertension in Patients with Coarctation of the Aorta

Walter M. Kirkendall, John W. Eckstein, and James W. Culbertson, Iowa City, Ia.

There is disagreement concerning the mechanism of the hypertension seen in coarctation of the aorta. One group believes that there is a generalized increase in peripheral arteriolar resistance and hypertension of the renal ischemia type in both upper and lower arterial compartments. The other group believes that there is no generalized increase in peripheral arteriolar resistance, and that the increase in mean blood pressure seen in the arterial compartment above the aortic constriction is due primarily to an increased stroke volume cardiac output into a shortened aortic compression chamber.

We have found that in the absence of cardiac failure there is an increased minute volume cardiac output (in 6 of 8 patients), and normal or decreased resistance to flow from the proximal aorta (in all 8). We did not find hypertension below the coarcted segment. In the splanchnic circuit blood flow was found to be normal or increased and arteriolar resistance normal or decreased. Renal blood flow was normal or increased, and renal vascular resistance was normal in 13 of 18 patients.

Clinical studies support the belief that coarctation of the aorta is not associated with renal type hypertension. Necrotizing arteriolitis seldom occurs in patients with coarctation (only 1 case report has been found in the literature). Pregnant women with coarctation of the aorta do not have the same incidence or type of complications as those with renal or essential hypertension. Coarctation patients seldom die in uremia, and when the coarctated segment is removed blood pressure in the arms frequently comes to normal—an unusual result in long-standing renal hypertension after nephrectomy. Thus, hemodynamic and clinical data indicate that human coarctation of the aorta is not associated with generalized arteriolar constriction and that the hypertension is not of the renal type.

Mechanisms Determining Reciprocal Beats Initiated by Ventricular Premature Systoles

Albert D. Kistin, Beckley, W. Va.

This study is stimulated by the recognition that retrograde conduction to the atria from ventricular premature systoles is common in man. Reciprocal beats initiated by ventricular premature systoles have been reported only rarely. Quantitative analysis of considerable data in 4 cases establishes mechanisms and throws additional light on other aspects of cardiac conduction. Simultaneous esophageal and standard electrocardiographic leads permit observations and measurements not otherwise possible. In 2 cases, the reciprocal beats would not otherwise be recognized, and in a third case the recognition is more firmly established.

The mechanisms are: (1) delayed V-A or A-V conduction permitting recovery of a common path and response to a returning impulse, (2) multiple pathways with different conduction times and refractory periods, (3) long preceding cardiac cycles, (4) early prematurity of ventricular systoles, (5) increased refractoriness and consequent delayed V-A conduction produced by a number of premature ventricular systoles in rapid succession, and (6) timing in relation to previous atrial and ventricular systoles, including the mechanisms of concealed conduction and supernormal phase.

The concept of multiple pathways is developed in particular. It has not been previously considered in clinical studies. There is recent experimental support for it as well as the clinical evidence presented here.

Two reciprocal cycles are observed in 1 case, and many cycles are observed in another producing paroxysmal tachycardia.

Action of Salyrganic Acid on the Electric and Mechanical Activities of the Isolated Guinea Pig Atria

Morris Kleinfeld, Edward Stein, and John Magin, New York, N. Y.

Guinea pig atria were suspended in Ringer-Locke solution and constantly oxygenated. The transmembrane potentials of right and left atrium were simultaneously recorded by means of intracellular microelectrodes, and correlated with mechanical activity. In 15 experiments the mechanical action was observed visually, and in 5 instances was recorded by means of a mechanoelectronic transducer for quantitative evaluation.

Salyrganic acid (mersalyl), an organic mercurial, was administered to bath solutions, in concentrations ranging between 1 and 4 mg. per 50 ml. of bath. The following changes were observed:

The earliest change was a moderate slowing of heart rate. This was usually followed by a decrease in mechanical action of both right and left atrium. Associated with this was an enhanced repolarization

of both transmembrane potentials. Depolarization, magnitude of the action potential and threshold potential were not significantly changed. In 16 of 20 experiments (80 per cent), the changes involving left atrium were more severe than right. Asystole usually occurred significantly earlier in the left atrium. Once asystole of the atria occurred, it was usually irreversible without treatment or when replaced in Ringer-Locke solution.

In 9 experiments, 100 mg. of cysteine was added to the bath 20 to 40 minutes after asystole occurred. In 8 of 9 instances (88 per cent), both the mechanical and electric changes showed gradual improvement with return to control levels in 50 per cent.

The findings suggest that salyrganic acid probably acts as a sulfhydril inhibitor and can be counteracted by administration of cysteine, an amino acid containing sulfhydril groups. The enhanced repolarization has been previously observed with other sulfhydril inhibitors, and it has also been postulated that it is associated with an increased rate of migration of K^+ from the cell.

These findings suggest a possible clinical application of cysteine in cases of mercurial intoxication in the course of congestive heart failure.

Alterations in Pulmonary and Peripheral Vascular Resistance in Hypothermia

Leslie A. Kuhn, New York, N. Y., and John K. Turner, Fort Knox, Ky.

The effects of immersion hypothermia on the systemic and pulmonary circulations were investigated in 58 dogs. Studies were made of electrocardiographic changes, oxygen consumption, cardiac output, rate of cooling, right atrial, peripheral arterial, pulmonary arterial and pulmonary "capillary" pressures, hematocrit, eosinophil count, pulmonary and systemic vascular resistance, and ventricular work in 36 untreated, anesthetized dogs; in 9 dogs receiving the pressor substance, l-norepinephrine; in 6 dogs receiving the sympatholytic agent, Dibenzyline-(N phenoxylisopropyl-N-benzyl-B chloroethylamine hydrochloride); in 5 dogs receiving Priscoline (2-benzyl imidazoline hydrochloride); and in 2 dogs which had been cold-adapted to a temperature of 5 C. for 2 months prior to the experiments.

Both pulmonary and systemic vascular resistances were progressively elevated during hypothermia, pulmonary resistance to a relatively higher degree than systemic resistance. Normal dogs surviving hypothermia below 22 C. in general demonstrated a higher peripheral vascular resistance and a lower pulmonary resistance than dogs manifesting ventricular fibrillation above 22 C. The sympathomimetic agent, norepinephrine, lowered the temperature to which dogs could be safely brought whereas the sympatholytic agent, Dibenzyline, acted deleteriously in that death in ventricular fibrillation occurred at higher temperatures than in untreated dogs.

The high pulmonary resistance in hypothermia was associated with maintenance of a high degree of right ventricular work, whereas the work of the left ventricle declined to a greater extent than that of the right. Attempts to significantly alter pulmonary arterial pressure and vascular resistance during hypothermia were unsuccessful. Cold-adaptation did not protect against ventricular fibrillation in hypothermia.

Effects of Intravenous Fat Infusion on the Blood Oxygen Exchange and Coronary Circulation

Peter T. Kuo,† Arthur F. Whereat, and Arthur A Altman, Philadelphia, Pa.

The effects of intravenous infusion of commercial fat emulsions and concentrated lipemic plasma on arterial oxygen saturation, coronary blood flow, cardiac output, and cardiac oxygen consumption were studied by right heart and coronary sinus catheterizations on 20 dogs in whom myocardial infarction had been produced by ligating one or more branches of the left anterior descending coronary artery 4 to 25 days previously. Similar catheterization studies were made on 10 normal animals.

A 7.5 to 11.4 mEq. per L. rise in serum total esterified fatty acids followed the intravenous fat infusions. The increase in serum fatty acids was accompanied, in the animals with myocardial infarctions, by the following changes: A mean decrease of cardiac output of 3.19 to 2.66 L. per minute, a mean decrease of coronary blood flow, of 87.5 to 66.3 ml. per minute, a mean decrease of oxygen consumption from 11.0 to 7.3 ml. per minute, and a mean decrease of 7.2 per cent in arterial oxygen saturation. The degree of arterial saturation decrease following fat injection appeared to have a direct correlation with the degree of myocardial insufficiency present in these animals. However, a mean decrease of 5.0 per cent in arterial oxygen saturation following fat infusion was also observed in dogs with intact coronary circulation; but these normal animals also showed a slight but insignificant increase in the cardiac output and coronary flow after fat infusion. Injection of the fat-free emulsion base (containing lecithin and 5 per cent dextrose) to 3 animals with and 3 without myocardial infarction caused no change in their blood oxygenation and coronary circulation from the control levels.

Surgical Correction of Chronic Mitral Insufficiency in Dogs

Sam J. Kuykendall, F. Henry Ellis, Jr., and John H. Grindlay, Rochester, Minn.

Technics for the correction of mitral insufficiency have been tested by most investigators in animal

in which mitral regurgitation has been created acutely. The pathologic defects in such animals are not comparable to the shortened posterior leaflet and dilated mitral ring seen in human beings who have the condition in question.

Mitral insufficiency which was progressive in degree was created in a series of 12 dogs by a method previously reported. Correction of the insufficiency was carried out 2 to 6 months later. Two methods were used to afford comparison, a circumferential suture of the mitral ring, and a distorting or reefing suture in the posterior portion of the mitral ring which does not enter the heart chamber. The adequacy of initial correction, the abatement of clinical manifestations of cardiac disease, and the findings at reoperation and necropsy 2 to 12 months after correction of the insufficiency were compared

Five of the 6 dogs in which the regurgitation was corrected by the circumferential suture were found to have significant recurrence of regurgitation. Only 1 of the 6 dogs in which the regurgitation was corrected by the distortion suture showed significant recurrence of regurgitation.

In dogs with acute regurgitation and normal mitral rings, both technics adequately correct the regurgitation. However, in the presence of chronic mitral insufficiency with dilated mitral rings, the circumferential suture did not maintain correction of the regurgitation as well as did the distortion suture in this series of animals.

Lung Compliance Studies in Pulmonary Heart Disease and Emphysema and in Normal Subjects

William J. Kuzman, Los Angeles, Calif., Herman F. Froeb, Lajolla, Calif., and Hurley L. Motley, Los Angeles, Calif.

Resting pulmonary compliance was determined in the sitting position, utilizing several simplified modifications of the continuous cycling method. The 81 subjects studied were arranged in 4 categories on a basis of the history and physical, radiographic and electrocardiographic examinations and pulmonary function studies. Group I consisted of 24 normals. Group II consisted of 9 patients with congenital cardiac lesions or acquired defects involving the left heart. Group III included 18 patients with pulmonary disability secondary to asthma, obstructive emphysema, cystic emphysema, sarcoidosis, asbestosis, recent smoke exposure, tuberculosis, kyphoscoliosis, and idiopathic fibrosis. Group IV consisted of 30 patients with far advanced pulmonary disability and associated pulmonary heart disease. Arbitrary figures of a resting arterial oxygen saturation above 92 per cent and an exercise oxygen uptake above 400 ml. per minute per M_2 per BSA were used for group III to separate it from group IV.

The mean pulmonary compliance for group I was 0.167 L. per cm. H_2O (S.D. $\pm$ 0.069 L. per cm. H_2O). The reproducibility of the method in 45 patients revealed a standard deviation of 0.012 L. per cm. H_2O. The range of normal values varied from 0.075 to 0.304 L. per cm. H_2O. In group II the mean compliance value was 0.155 L. per cm. H_2O (S.D. $\pm$0.068 L. per cm. H_2O) with a range from 0.048 to 0.246 L. per cm. H_2O. In group III the mean compliance was 0.152 L. per cm. H_2O (S.D. $\pm$0.067 L. per cm. H_2O) with a range from 0.075 to 0.277 L. per cm. H_2O. In group IV the mean compliance was 0.083 L. per cm. H_2O (S.D. $\pm$.050 L. per cm. H_2O) with a range from 0.013 to 0.197 L. per cm. H_2O.

Pulmonary compliance was best correlated with total vital capacity from a battery of pulmonary function tests, both in the normals and abnormals. Some correlation was noted between compliance and the uniformity of alveolar mixing and the arterial pO_2. No correlation was noted between pulmonary compliance and timed vital capacity, maximal breathing capacity, ratio of residual to total lung capacity, and the arterial oxygen saturation. The compliance value was decreased as respiratory rate was increased, and the resting work of breathing was significantly elevated in patients with pulmonary heart disease.

Anisindione: A New Anticoagulant with Unusual Properties

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Anisindione (2-p-anisyl indandione-1,3) is an anticoagulant of the indandione type which is readily soluble in water, tasteless, and rapidly absorbed from the intestinal tract. When 500 mg. are given orally, the prothrombin level falls rapidly to 50 per cent in 6 hours. Thereafter, it decreases more slowly until levels between 15 to 30 per cent are reached in 32 to 72 hours.

The response to the drug is unusually uniform and predictable. The effect is almost self-limiting, since dangerously low prothrombin levels can only be reached with enormous amounts of the drug. Maintenance of therapeutically decreased prothrombin activity can be achieved by one dose of 250 mg. of the drug every third day. This maintenance dose is again unusually uniform in almost all cases.

The effect of the drug can be rapidly interrupted by the use of phytonadione (Mephyton). After interruption of the anticoagulant effect by phytonadione, the depression of prothrombin activity can be restored rapidly, usually within 36 hours.

Patients previously treated with Dicumarol can be transferred to anisindione maintenance without restarting therapy with induction doses. No side-effects or hypersensitivities have been noted in this study. Altogether, the drug has been given for 1,615 patient-days to 65 patients. There was one episode of shortlasting hematuria in this study. The drug

appears to be a safe and predictable anticoagulant which lends itself to simple management.

Chlorothiazide in the Management of Edema of Heart Failure, Nephrosis, and Cirrhosis

John H. Laragh and Felix E. Demartini, New York, N. Y.

Chlorothiazide is a substituted benzothiadiazine compound with a free sulfonamide group. In animals it markedly alters renal transport of chloride sodium and potassium. Chlorothiazide was studied in advanced heart failure, cirrhosis with ascites and nephrosis. Patients were placed on a carefully controlled constant regimen on the metabolic ward. Electrolyte balance, blood chlorothiazide levels, uric acid balance and urinary aldosterone were measured. Thirty-four hospital patients were studied. Fourteen of 15 patients with cardiac failure exhibited considerable sodium chloride diuresis. Four had demonstrated failure of response to mercurial diuretics. In cirrhosis, complete diuresis of ascites was accomplished in patients refractory to mercurials; chlorothiazide was effective in 6 of 8 instances. Five of 6 nephrotic patients had striking diuresis when all other measures had failed. Five patients with cor pulmonale continued to respond despite markedly reduced plasma chloride.

Chlorothiazide, like para-aminohippurate, is secreted by the renal tubule. It does not appear to exert specific effects on glomerular filtration rate. Maximal therapeutic effects occurred with plasma concentrations of less than 0.1 mg. per cent. Chlorothiazide appears to inhibit renal tubular reabsorption of electrolyte in a manner different from other known agents. The existence of at least 2 separate renal mechanisms for sodium and/or chloride reabsorbtion is suggested by observations that chlorothiazide effects were additive to those of a mercurial or to those of a carbonic anhydrase inhibitor, were independent of plasma chloride and were noted in mercurial-resistant patients. Continued administration may lead to hypokalemic, hypochloremic alkalosis with elevated pCO_2; these effects were readily reversed by KCl. At times blood uric acid may be elevated.

No toxocity was observed and refractoriness did not usually develop. Chlorothiazide is an effective oral agent for treatment of edema. Its pharmacologic effects on ion transport allow a rational approach to electrolyte and water derangements of heart failure.

Clinical and Pathologic Studies of Anginal Pain in Congenital Cardiac Lesions Affecting the Right Ventricle

Richard P. Lasser and Gabriel Genkins, New York, N. Y.

An indication that coronary flow to the right ventricle might be inadequate in persons with various congenital cardiac defects causing right ventricular hypertrophy was furnished by the clinical observation of anginal pain, and pathologic observation of diffuse and extensive right ventricular myocardial fibrosis. In addition to midsternal constriction and pain caused by effort and relieved by rest, paroxysms of severe anterior chest pain of protracted duration were observed which were not necessarily precipitated by effort nor relieved by rest.

Cardiac catheterization studies in 9 cases revealed the presence of marked right ventricular hypertension, approximating or exceeding systemic pressure as a common denominator in all cases. The lesions observed were: isolated pulmonic stenosis in 5 patients, tetralogy of Fallot in 1, patent ductus with reversed flow in 1, interventricular septal defect with pulmonic hypertension in 1, and transposition of the great vessels in 1.

Electrocardiograms showed pronounced right ventricular hypertrophy, generally with depression of the S-T segments and inversion of T waves in V_1 to V_3. Exercise tests in 2 cases reproduced chest pain.

Postmortem examination in 4 cases demonstrated that the hypertrophied right ventricle showed the presence of scattered areas of myocardial fibrosis whereas the left ventricle did not. The appearance was that generally considered to indicate the existence of myocardial ischemia. Coronary vessels were stated to be patent throughout. The occurrence of myocardial fibrosis and its localization to the right ventricle suggested that the anginal pain was due to right ventricular ischemia.

The contributory factors are believed to be: 1. Markedly elevated right ventricular stroke work resulting in high oxygen demand. 2. Arterial desaturation. 3. Greatly elevated right ventricular intracavitary and intramural systolic pressure, and elevated right atrial and ventricular diastolic acting to reduce the coronary perfusion gradient during systole and diastole. The favorable response of this pain to pulmonary valvulotomy was quite dramatic in several cases with isolated pulmonic stenosis.

Preparation and Use of Handmade Plastic Prosthesis in Vascular Surgery

Abel A. Lazzarini, Jr.† and Jere W. Lord, Jr., New York, N. Y.

The use of plastic prostheses for permanent replacement of blood vessels has increased in the last few years. This has mainly been due to difficulties encountered in the procurement and preservation of suitable homografts. This paper will describe our results in the evaluation of different types of experimental plastic prostheses for periods up to 15 months. The replacements were compared with fresh and preserved auto- and homografts in the same recipient. Practical aspects in the preparation of some of these prostheses will be emphasized. Satisfactory results were obtained when all "finishings"

were eliminated by careful rinsing with a strong neutral detergent and then coating the fiber with silicone solutions. The segment to be replaced was measured directly at surgery and a tube of fabric of appropriate diameter, but longer than necessary, was made with the use of a special sewing machine with a double zigzag suture. The prostheses were sterilized and rinsed in isotonic salt solutions and then divided to facilitate the preparation of the proximal and distal anastomoses. Adequate tension was finally obtained by suturing the 2 segments of the prostheses together. It is evident that the surgical implantation of plastic vascular replacements is difficult, and we believe that the removal of foreign material, the treatment of the surface of the prostheses with blood repellents and avoidance of any significant difference in length or diameter will yield more consistent results.

Substernal Transaortic Coronary Arteriography: Introduction of a Clinical Technic

William M. Lemmon, J. Stauffer Lehman, and William Likoff, Philadelphia, Pa.

Although coronary artery atherosclerosis may be a diffuse vascular disease, pathologically the most important, if not the most common, lesion is located in the first 4 to 6 cm. of the origin of the vessel. In view of this segmental distribution, an urgent need exists for a safe and simple method of contrast visualization of the coronary arteries. An experience with a technic is reported which in clinical application has achieved certain fairly satisfactory visualizations of the main divisions of the coronary tree.

The procedure is carried out, after premedication, under aseptic technic and under local anesthesia. The patient is positioned, with markers taped to the chest, and a "scout film" is taken to determine the required direction and depth of needle puncture. The Lehman needle is introduced into the ascending aorta from the suprasternal notch; the tip rests free in the aortic lumen above the sinuses of Valsalva. At this point if it is desirable to determine a gradient across the aortic valve, a second needle is introduced into the left ventricle utilizing a subxiphoid approach. The second needle is removed once the desired pressures are obtained. A contrast medium is rapidly injected by the mechanical Lehman injector into the aortic lumen through the substernal needle, and a series of films is taken at one half second intervals at an exposure time of one thirtieth of a second. Immediately upon completion of the radio-opaque injection the needle is removed.

The morbidity accruing from this type of precise diagnostic study has been negligible. While the degree of coronary opacification has been variable, certain satisfactory visualizations have been achieved.

Pulmonary Vascular Resistance in Man at Different Intravascular Distending Pressures, Measured in a Case of Mitral Stenosis Complicated by Anomalous Pulmonary Venous Connection

Bess L. Lendrum and A. M. Lichtman, Chicago, Ill.

The factors capable of altering pulmonary vascular resistance in man have not been entirely clarified, despite numerous studies. Pulmonary vascular resistance was therefore studied in a case of mitral stenosis, complicated by partial anomalous pulmonary venous drainage of almost the entire right lung to the superior vena cava. The resistance was calculated in the usual manner, using the simple relationship $R = P/F$, where R represents the vascular resistance, P the pressure gradient between the pulmonary artery and the pulmonary vein, and F the rate of blood flow.

Pulmonary hypertension and a markedly elevated left atrial pressure were found to be present. The data obtained suggest that the blood flow through all lung segments was approximately equal. The pressure gradient across the anomalously draining lung was roughly 3 times that across the lung draining to the left atrium, yet the flow through each lung was approximately the same. The conclusion was drawn that the pulmonary vascular resistance in the lung draining to the left atrium was ⅓ that in the lung draining to the superior vena cava. Based on these findings and observations in experimental animals, it is possible that the decreased vascular resistance of the lung draining to the left atrium can be attributed, at least in part, to passive dilatation by the high left atrial pressure.

Calcification of the Ascending Aorta: A Study of its Diagnostic Specificity for Luetic Aortitis

James J. Leonard and Kenneth M. Moser, Washington, D. C.

During the past 18 months, a comprehensive investigation has been carried out to define the specificity of calcification of the ascending aorta as a diagnostic sign in luetic aortitis.

All admission chest roentgenograms were reviewed daily. When ascending aortic calcification was noted, a sequential program of study was followed. The presence of calcification, when at all equivocal, was confirmed by further radiologic study.

A routine serologic test (VDRL) was first obtained. When this test proved negative or doubtful, the Venereal Disease Control Division of the hospital was contacted. This unit searched its comprehensive files. A patient was classed as having a "positive history" only when a positive serology in blood or spinal fluid, or an unequivocal primary or secondary luetic lesion, had previously

been identified. If both serologic and historic data were negative, a Treponemal Immobilization Test (TPI) was performed.

Sixty-nine patients with calcification of the ascending aorta were discovered. The mean age of this group was 64.5 years (range 42 to 94 years). However, 6 (9 per cent) were below age 50, and 18 (26 per cent) were below 60. Fifty-two (75.4 per cent) of these individuals had a positive serologic blood test. Of 17 with negative serology, however, 6 (8.7 per cent) had a positive luetic history and four (5.8 per cent) had a positive TPI test. Thus, 62 (89.9 per cent) of those with calcification of the ascending aorta were identified as luetic subjects. This represents a minimal figure since only 1 of the 7 (10.1 per cent) "nonluetic" subjects had a TPI test, the remainder having left the hospital before the test was performed. Therefore, calcification of the ascending aorta was a "false positive" sign for luetic aortitis in only 1 (1.6 per cent) of the 63 patients in whom complete data were obtained.

On the basis of this study, it is concluded that calcification of the ascending aorta is a valuable diagnostic sign in luetic aortitis, exhibiting a high degree of specificity.

Observations on the Significance of the Delayed Appearance of the First Heart Sound in Mitral Stenosis

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The Q-1 time is a measure of the interval between the beginning of ventricular excitation and the first rapid vibrations of the first heart sound. This interval has been found to be prolonged in mitral stenosis and consequently serves as a diagnostic adjunct in the evaluation of mitral valvular disease. Recent observations on the genesis of the atrial gallop sound in hypertensive disease has revealed a prolongation of the Q-1 time in a majority of patients with severe forms of this disease. The present study was undertaken in an attempt to determine the extent and nature of this finding.

Simultaneously recorded electrocardiograms and logarithmic phonocardiograms were obtained in 25 consecutive patients with hypertensive vascular disease. All of the patients had sustained diastolic hypertension of 110 mm. Hg or greater, and 24 had electrocardiographic and roentgenographic evidence of cardiac enlargement. Individuals with first degree heart block or bundle-branch block were not included. Q-1 time was measured from the onset of the Q-wave in the standard limb leads to the initial high amplitude rapid vibrations of the first heart sound. Normal sinus rhythm was present in all cases and no corrections for R-R interval were made.

The Q-1 interval in a group of 18 normal individuals measured in this manner was .055 seconds (S.D. ±.003). In the hypertensive group, the mean Q-1 time was .07 seconds (S.D. ±.01). Thirteen of the 25 patients had Q-1 times of .07 seconds or greater, the figure frequently accepted as the highest limit of normal. The mean R-R interval for the group was .80 seconds.

These data are of particular significance in the phonocardiographic evaluation of mitral valvular disease where prolongation of the Q-1 interval cannot always be attributed to valvular stenosis. The delay in appearance of the first heart sound is of additional interest in that it in part explains the frequent occurrence of an audible atrial gallop in hypertensive vascular disease.

Correlation Between the Electrocardiogram and the Transmembrane Action Potential in Potassium and Calcium Deficiency of the Mammalian Heart

Eugene Lepeschkin,† Borys Surawicz, Herman C. Herrlich, Burlington, Vt., and Brian F. Hoffman, New York, N. Y.

Twenty isolated rabbit hearts were perfused with Krebs-Henseleit solution deficient in potassium, calcium, or both. Electrocardiograms were recorded simultaneously with monophasic action potentials obtained by means of the suction electrode, and, in some experiments, with the intraventricular pressure curve. In 5 experiments, the intracellular action potentials obtained with a flexibly mounted microelectrode were recorded simultaneously. They showed the same changes as the action potentials obtained with the suction electrode. Perfusion with potassium-free solution caused a progressive increase in duration and decrease in steepness of the descending branch of the action potential; the electrocardiogram showed increase in duration of the T wave but not of the S-T segment. Later the plateau of the action potential became shorter and steeper while the descending limb continued to become longer and flatter until the repolarization segment of the action potential became concave; the electrocardiogram showed a T wave of short duration, followed by a long wave which extended considerably beyond the end of mechanical contraction (U wave). Perfusion with calcium-free solution did not decrease the steepness of the descending limb of the action potential, but increased the duration of the plateau. The electrocardiogram showed a progressive lengthening of the S-T segment without change in duration of the T wave. The mechanical contraction showed a corresponding increase in duration and progressive decrease in amplitude. Perfusion with solution without potassium and calcium caused lengthening of the plateau as well as a lengthening and flattening of the descending limb

of the action potential. The electrocardiogram showed prolongation of the S-T segment and the T wave. It was concluded that electrocardiographic changes of hypopotassemia and hypocalcemia result from specific alterations of the repolarization process at the cellular level.

Semiquantitative Histopathologic Method for Studying the Entire Heart for Electrocardiographic Correlation

Maurice Lev and James B. McMillan, Miami Beach, Fla.

We have evolved the following method of studying the heart for electrocardiographic correlation. This method yields semiquantitative data of the entire conduction system, and of the myocardium of the proximal and distal portions of each wall of the atria and ventricles.

The heart is opened at autopsy by a modification of the Mönckeberg-Oppenheimer method. The coronary arteries are then opened by a combination of dissection and cross-sectioning. The heart is fixed in neutral formalin for 48 hours and all chambers are then photographed. The aorta is now cut away at the upper margins of the sinuses of Valsalva. The S-A node and its approaches are then placed in 1 block, serially sectioned, and every twentieth section is retained. A second block is made from the right atrial appendage and the superior wall of the right atrium, containing the ramus ostii cavae superioris, the blood supply to the S-A node. This is cut serially, and every twentieth section is retained. The anterior and inferior walls of both atria and ventricles are now removed from the atrial and ventricular septa. The A-V node, bundle and bundle branches, including the ramus septi fibrosi, are now fashioned into 5 blocks and serially sectioned. Every twentieth section (through the A-V node and penetrating bundle) is retained in the first, every tenth section (through the branching bundle and bifurcation) in the second, and every twentieth section (through the bundle branches) is retained in the remaining blocks. The bases of the anterior and posterior papillary muscles of the left ventricle are now blocked, cut serially, and every fortieth section is retained. This leaves the proximal atrial septum, the most anterior and the apical portion of the ventricular septum, and the anterior and posterior walls of both atria and ventricles. These are completely fashioned into blocks, and 2 sections are cut from each block. All sections are stained alternately with hematoxylin-eosin and Weigert-Van Gieson stains.

This method of sectioning is now being used to create an anatomic base for electrocardiography.

Clinical Status of 200 Patients, 5 to 8 Years After Mitral Commissurotomy

William Likoff, Harry Goldberg, and Joseph Uricchio, Philadelphia, Pa.

Sufficient time now has elapsed for a precise evaluation of mitral commissurotomy. With this in view, the clinical status of the first 200 of our patients who have survived the operation for 5 to 8 years is reported. The individuals included in this study were operated on from 1948 to 1952. Each suffered from uncomplicated mitral stenosis. The left atrial appendage was the only surgical portal used.

Eight of every 10 patients who had been dyspneic remained free of that disability; 9 of every 10 with hemoptysis continued to be relieved; 5 of every 10 with peripheral edema did not suffer a recurrence.

In the majority of these individuals the objective changes were less striking. Beneficial alterations in the various auscultatory events are observed in only 4 of every 10 patients. The heart size decreased in only 2 of every 10 individuals.

These observations reaffirm the curious paradox noted in the earlier evaluations of mitral commissurotomy, namely, that symptomatic improvement is rarely attended by objective evidences of benefit. The explanation must reside with relationships which exist between the effective area of the mitral orifice and the symptomatic and objective aspects of stenosis. It is reasonable to suggest that commissurotomy, as practised during the interval of this study, generally accomplished a modest increase in the size of the mitral orifice, which was sufficient to alter the dynamic pattern of the lesion and the subjective status of the patient, but was too limited to alter the objective findings.

Recognition of these facts and acknowledgment of a 10 per cent incidence of restenosis does not condemn the surgical treatment of mitral stenosis, but adds impetus to the search for technics capable of increasing the size of the mitral orifice more extensively and with no added risk.

Paradox of Right Ventricular Enlargement in Mitral Insufficiency

William Likoff and Joseph Uricchio, Philadelphia, Pa.

The left heart bears the pathophysiologic burden accruing from free mitral insufficiency. Clinical experiences support this concept through the roentgenologic and electrocardiographic indications of left ventricular enlargement when the lesion occurs alone or in combination with minimal mitral stenosis. Thus, when right ventricular enlargement accompanies mitral insufficiency, it suggests the pres-

ence of an additional defect as the cause of the right ventricular hypertrophy.

The present report, based on a pursuit into the reliability of this generalization, has been derived from a study of 4 patients who were subjected to cardiac catheterization and to the surgical exploration of their mitral valves. It indicates, contrary to expectations, that significant and isolated mitral insufficiency can produce the roentgenologic and electrocardiographic evidences of right ventricular enlargement.

Evidence is offered to suggest that this paradox arises as the result of the physical characteristics of the left atrium. When this muscle fails to stretch in response to the augmented volume load produced by the regurgitation, the pressure within the chamber rises disproportionally. The exaggerated response is transmitted to the pulmonary circuit where it produces an effective stimulus for hypertrophy and fibrosis of the vascular wall. In brief, a tonic atrium may transfer the burden of mitral insufficiency from the left to the right ventricle through its effect on the pulmonary vascular tree.

Conversely, when the left atrium is converted to a large, passive and highly distensible structure, the devolutionary pathophysiologic effect of mitral regurgitation is restricted to the left heart.

Radioactive Fat Absorption Patterns: Significance in Coronary Artery Atherosclerosis

William Likoff, Donald Berkowitz, Asher Woldow, and Gerson Jacobs, Philadelphia, Pa.

Coronary artery atherosclerosis has been attributed to an inborn error of fat metabolism which cannot be precisely defined by any biochemical test.

Since Stanley and Thannhauser's experiments, I^{131}-triolein has been utilized to study fat metabolism. It has been demonstrated that the blood radioactivity in normal individuals reaches a peak level within 4 to 6 hours after the ingestion of a tagged fat meal. This peak level approximates 16 per cent of the dose taken. The value then falls, so that less than 5 per cent remains after 24 hours.

Under the conditions imposed by the test meal, the total blood radioactivity consists of 1 portion bound to lipid, and another combined with inorganic iodide. The inorganic portion is excreted into the urine where its concentration may be measured. During the period when the blood values are decreasing, the ratio of the inorganic to the organic radioactivity is inversely proportional to the total concentration. In contrast, the radioactivity in the urine increases.

This report concerns radioactive fat absorption patterns, obtained in patients less than 50 years of age, with coronary artery atherosclerosis as indicated by the occurrence of a previous myocardial infarction and/or unequivocal coronary artery insufficiency. The patterns show characteristic deviations from the normal. The peak radioactivity concentration is delayed, and is higher than in normal individuals. The fall in radioactivity is considerably prolonged, so that within a 24-hour period, marked retention is observed. This appears to be due to an abnormal rate of conversion of the organic to the inorganic fraction.

The constancy of these results appears to confirm the presence of a metabolic error in patients with coronary atherosclerosis. It suggests that this may be revealed by radioactive fat tolerance studies, even prior to the appearance of clinical manifestations such as angina or a myocardial infarction.

Simultaneous Measurement of Circulating Red Cell and Plasma Volumes in the Kidney

Lawrence S. Lilienfield and John C. Rose,† Washington, D. C.

In this study 17 pentobarbital anesthetized dogs were utilized. Through an abdominal incision the left kidney pedicle was mobilized and the renal vein connected through a length of polyethylene catheter to a catheter in a femoral vein. A mixture of Cr^{51} tagged red cells and I^{131} serum albumin was then injected rapidly into the renal artery. Total renal blood flow was collected continuously for 1 minute in 2-second samples from the renal vein catheter which had been disconnected from the femoral vein just prior to injection.

From an analysis of the washed red cell and plasma activities of the samples, the time-concentration curves of radioactivity of plasma (albumin) and red cells were separately constructed. From the mean transit times of the curves and the measured renal blood flow, the circulating red cell and plasma volumes of the kidney were calculated. In all experiments, measured mean arterial pressure was greater than 100 mm. Hg.

Circulating renal red cell volume averaged 10.8 ± 2.8 ml. per 100 Gm. of kidney over an arterial hematocrit range from 28 to 52. Assuming a circulating intrarenal hematocrit equal to the arterial hematocrit, this blood volume equivalent of the kidney averaged 22.7 ± 5.3 ml. per 100 Gm.

Circulating plasma (albumin) volumes per 100 Gm. averaged 14.0 ± 4.1 ml. in this group of experiments. Total renal blood volume calculated as the sum of the red cell and plasma volumes averaged 24.8 ± 5.5 ml. per 100 Gm.

These data support the concept of a lower intrarenal hematocrit than that of arterial or venous blood. The rapidly circulating (1 minute) volume of distribution of albumin in the kidney is slightly in excess of that expected from the arterial hematocrit and renal red cell volume.

Response of Normal Children and Those with Cardiac Disease to Exercise Tests Using the Bicycle Ergometer

Leonard M. Linde, Forrest H. Adams, and Eduardo C. Borda, Los Angeles, Calif.

In the clinical examination of children with heart disease, evaluation of the actual physical limitation is often difficult. In an attempt to measure objectively decreased exercise tolerance in such patients, tests were performed using a bicycle ergometer.

Two hundred sixty-three normal healthy children, ranging from 6 to 15 years of age, were placed on a bicycle ergometer set at a previously determined workload. Measurements were made of the blood pressure, pulse and respiratory rate at rest, at 2-minute intervals during the work and finally 2 minutes after the work. The height, weight and vital capacity were also measured in each subject. Identical studies were then performed on children with various forms of heart disease.

The response of normal children to work on a bicycle ergometer revealed marked individual variation, even when age, height, weight, or surface area were considered. Patients with compensated cardiac conditions performed in a manner indistinguishable from the normal. Severe cardiac incapacity was essential before significant deviation could be detected.

Extensive physiologic data and standards for height, weight, surface area, blood pressure and vital capacity for the age group of 6 to 15 years were obtained in the course of the study.

Mitral Insufficiency and Pulmonary Hypertension Accompanying Patent Ductus Arteriosus

Leonard M. Linde, Burton W. Fink, and Forrest H. Adams, Los Angeles, Calif.

The clinical diagnosis of uncomplicated patent ductus arteriosus (PDA) is not difficult, but when this defect exists in association with other cardiovascular anomalies, the classical signs are often absent. This report presents 3 children with the previously unreported triad of mitral insufficiency and pulmonary hypertension in association with PDA. Clinical and laboratory findings, physiologic data and difficulties encountered in definitive diagnosis will be discussed.

The patients, all females, each presented with marked cardiomegaly, an accentuated pulmonary second sound and a grade III to IV blowing systolic murmur along the lower left sternal border transmitted to the apex. Radiographic examination uniformly showed enlargement of all 4 cardiac chambers and marked pulmonary vascular engorgement. The electrocardiogram of each girl was consistent with biventricular hypertrophy. In each case, right heart catheterization revealed a left-to-right shunt via a PDA and marked pulmonary hypertension. In 1 patient, angiocardiographic evidence of ventricular washout of an enlarged opacified left atrium graphically demonstrated mitral insufficiency.

At surgery, a large PDA was ligated in each of the 3 girls. Lung biopsies at that time revealed moderate medial hypertrophy and mild intimal proliferation of pulmonary arterioles.

Postoperatively, marked improvement was noted in all. The systolic cardiac murmur had now become higher pitched, grade III to IV, blowing and maximal at the apex, increased in the left lateral position, and well transmitted to the left axilla. Recatheterization in 1 patient revealed normal right ventricular pressure, and studies in all showed markedly decreased right ventricular hypertrophy, some decrease in left ventricular enlargement and normal pulmonary vascularity.

Failure to perform cardiac catheterization and an initial recommendation of watchful waiting in these children might have had disastrous results. Recognition of this described triad, differential diagnosis from interventricular septal defect, and surgical closure of the PDA before development of irreversible pulmonary hypertension, is of the utmost importance.

Cardiac Effects of Sympathomimetic Amines in Experimental Complete Heart Block

Arthur J. Linenthal, Paul M. Zoll, Leona R. Norman, William Gibson, and Hussein A. Shustari, Boston, Mass.

The chronotropic action of sympathomimetic amines on the ventricle is of great clinical importance: it may represent a therapeutic effect in Stokes-Adams disease or a toxic effect in shock. Delineation of this action is incomplete because it is normally masked by sinoatrial rhythm, and clinical studies in complete heart block are necessarily limited. Drugs were therefore studied in dogs with chronic complete heart block produced surgically.

Epinephrine and isoproterenol both accelerated the idioventricular pacemaker, and reproducible S-shaped dose-response curves were obtained with doses ranging from 0.01 to 100 μg. per Kg. Maximal acceleration of 77 per cent was reached with isoproterenol and of 69 per cent with epinephrine. Toxic effects of ectopic ventricular tachycardia or fibrillation were reached with doses of each drug that were 10 to 100 times the doses that produced significant acceleration of 30 per cent. Ventricular fibrillation was terminated by external electric countershock so that drug studies could be continued in the same animal. From these observations,

there is little choice between the 2 drugs in Stokes-Adams disease: both are potent accelerators of ventricular rhythmicity and have similar wide therapeutic/toxic ratios. Previously, we came to similar conclusions in studies of patients with persistent absence of intrinsic ventricular activity kept alive by external electric stimulation. Epinephrine usually raised the blood pressure, whereas isoproterenol did not.

Many vasopressor agents used in the treatment of shock are thought not to stimulate the heart. However, we observed that levarterenol, phenylephrine, metaraminol, mephenteramine, and methoxamine, all widely used potent vasopressor agents, had markedly different effects on ventricular rhythmicity. Levarterenol, for example, produced ventricular acceleration and tachycardia. Methoxamine unexpectedly produced significant ventricular slowing and ectopic activity even when vagal effects were blocked by atropine. Choice of a sympathomimetic agent for the treatment of shock requires consideration of these varying, potentially toxic chronotropic effects.

Theorem Generalizing the Einthoven Triangle and the Wilson Central Terminal

Bernard A. Lippmann, Brooklyn, N. Y.

The Einthoven triangle and the Wilson central terminal are both somewhat more valuable in electrocardiography than one would expect. The difficulty is that, although these constructs are applied to the human body, their theoretical justification rests on a model that is quite different; it replaces the body by a sphere and fills the interior with an homogeneous, isotropic, conducting medium. Yet, despite the drastically simplified structure of this model, the theoretical deductions from it apply, in fair approximation, to the more complex electric situation that an actual body presents.

This suggests that the model may be unnecessarily simplified. Its special characteristics may have been dictated by mathematical convenience rather than by anything inherent in the physics of the problem, and perhaps the same conclusions are implied by a more complicated, and thereby by a more realistic, model.

In the present paper, we confirm this conjecture. We show that the customary properties ascribed to the Einthoven triangle and the Wilson central terminal may be derived from a model that is arbitrarily inhomogeneous and anisotropic, and has a surface of any shape, provided that 2 requirements are satisfied: (1) that any plane equidistant from 2 apices of the Einthoven triangle is a plane of symmetry, and (2) that if an axis is passed through the center of the Einthoven triangle, perpendicular to its plane, the model presents the same aspect before and after a rotation of 120° about this axis.

Although this generalization of the usual model employed in electrocardiography is the main contribution of this paper, the present treatment is novel in one other respect—the method of analysis is entirely nonmathematical and is concerned only with the symmetry properties of the model. We hope that this illustration of the power of symmetry analysis will stimulate the wider use of such analytic methods.

Effects of High Altitude on the Cardiovascular System

Philip Lisan, Philadelphia, Pa., Warren L. Eddington, Houston, Tex., and Kenneth E. Pletcher, Burderop Park, England.

Control subjects were completely evaluated, and simulated runs made up to 30,000 feet with recordings of electrocardiograms and ballistocardiograms which were all normal both at ground level and at altitude. The control subjects were also studied in partial pressure suits and helmets at 65,000 feet, and evidence of altered cardiovascular hemodynamics was intimated. Several cases of altitude dysbarism were studied immediately following the acute episode, and at a later date under simulated flight conditions. These latter patients revealed disintegration of their ballistocardiograms only, which one might deduce to be the result of diminished cardiac output and altered peripheral vascular status. It is hypothesized that anoxia and hypoxia of altitude produces reduction in coronary artery flow, with diminished cardiac efficacy and resulting diminished cardiac output producing the various types of altitude dysbarism in certain individuals. A BCG might be a simple and yet adequate instrument for predicting the probability of future altitude reactions in this latter group at simulated altitudes.

Comparison Between Electrokymograms of Left Atrium and Left Atrial Pressure Patterns in Lesions of the Mitral Valve

Chi K. Liu and Aldo A. Luisada, Chicago, Ill.

A comparative study of left atrial pressure tracings and left atrial electrokymograms was made in 17 cases. The obtained data were correlated with the clinical findings, the electro- and phonocardiographic tracings, and the roentgenologic picture. The degree of mitral stenosis was evaluated on the basis of the diastolic gradient between left ventricle and left atrium.

Study of the pressure pattern of the left atrium in normal animals and normal humans revealed that, during ejection, a drop in pressure takes place. Therefore, whenever the pressure rose in the left atrium during ejection, it was admitted that there was mitral regurgitation. From this was evolved the concept of the mean systolic elevation.

Three main patterns were observed in mitral patients: 1. Normal pattern or giant A wave was found in pure mitral stenosis. 2. A plateau pattern was found in cases with mitral stenosis and insufficiency. Data indicating that the plateau was due to transmission of left ventricular pressure to the left atrium (i.e., mitral regurgitation) were presented. 3. A late-systolic wave was found in pure mitral insufficiency. Reasons why this wave should be called I wave (insufficiency wave) are given. This wave may occasionally fuse with the normal V wave or may have a peak before the end of systole.

A comparison of the electrokymographic patterns with those of left atrial pressure revealed that there was a substantial coincidence between the two in 13 out of 17 cases.

A correctly recorded and interpreted left atrial pressure pattern is the most useful and significant laboratory finding in cases of mitral valve disease. Considering the ease and harmlessness of EKY recordings, it was concluded that they should be taken systematically in all mitral valve patients.

Syndrome of Stenosis of the Right Pulmonary Artery

Joseph Lloyd-D'Silva, Robert F. Dillon, and Benjamin M. Gasul, Chicago, Ill.

Stenosis of the pulmonary arteries is a rare anomaly. There have been few published reports, most of them describing multiple stenoses in one or both branches of the pulmonary artery. The purpose of this paper is to report on 5 patients who manifested clinical evidence of stenosis of the right pulmonary artery, confirmed by cardiac catheterization and angiocardiographic studies.

The embryologic development of the right pulmonary arch and the factors responsible for its involution are briefly described. The fact that absence or isolated stenosis of the pulmonary artery has been reported more often on the right leads us to believe that there is a common embryologic explanation for both these anomalies. Stenosis may properly be regarded as an intermediate stage between atresia and normal development of the pulmonary artery.

The patients ranged in age from 16 months to 15 years, and 4 of the 5 had an associated patent ductus arteriosus. All patients had detailed clinical, roentgenologic, angiocardiographic and hemodynamic studies. In order to assess the effect of the stenotic pulmonary artery alone, clinical, electrocardiographic, roentgenologic and hemodynamic data were obtained after surgical interruption of the ductus. The diagnostic problems created by the coexistence of this malformation are pointed out.

The characteristic findings were a grade III to IV systolic murmur over the base of the heart, evidence of decreased vascularity of the right lung field on routine roentgenogram, disproportionate opacification of the 2 lung fields on the dextroangiocardiogram and mild to moderate pulmonary hypertension proximal to the stenosis with a pressure gradient across the stenotic area. The diagnostic problems created by the coexistence of this malformation with others are pointed out.

Resonance of Pulsations in Elastic Tubes

Harry Lobel, Omaha, Neb.

From the viewpoint of analog computations, the flow of blood is subject to two types of laws: laws of hydraulics and laws of resonance. To separate the effects of these laws, pulsations are introduced into elastic tubes filled with fluid. Tubes with various diameters and various wall thicknesses are employed. At the proper frequency the pulsations become resonant or tuned. The resonant frequency depends on the elasticity of the tube; the more rigid the wall, the higher the frequency. With similar wall thicknesses, larger circumferences mean lower frequencies. With similar circumferences, thicker walls mean higher frequencies. Simple elastic tubes are dynamically similar and have the same resonant frequency, provided that the ratio between wall thickness and circumference is the same. In resonance, pressure and flow correspond. In dissonance, pressure is excessive in relation to flow. There are 2 kinds of pressure in dissonance: one is an effective pressure which drives the fluid; the other is an ineffective, destructive back-pressure which expends itself against the walls of the tube. This back-pressure is readily demonstrable, and is due to impedance. Impedance, as differentiated from resistance, is a characteristic of dissonant flow. In a pulsating hydraulic system, impedance causes loss of efficiency, excessive pressure, increased impact on the tube, and strain on the pump. A low-pressure system in dissonance is subject to greater strain than a high-pressure system in resonance. To correlate pressure-flow relationships, there must be a correction for the presence of impedance. There are indications that the circulation is normally resonant, but in some disorders, such as hypertension, it becomes dissonant. Impedance, due to dissonance, may be a destructive factor in hypertension. An instrument for the clinical measurement of impedance in the arteries is feasible and may be of diagnostic value.

Effects of Digitalis on Distribution of Body Potassium and Sodium

Bernard Lown, Gerald H. Whipple, Louis C. Craig, Boston, Mass., George McLemore, New York, N. Y., and Samuel A. Levine, Boston, Mass.

Rapid digitalization alters the distribution of body sodium and potassium. Tissues other than

the heart are primarily responsible for these electrolyte shifts.

Forty dogs were digitalized 110 times by fractional intravenous doses of acetylstrophantl.idin to an end point of ventricular tachycardia. A rise in arterial serum potassium occurred in 93 per cent (102/110) of digitalizations averaging 0.64 mEq. per L., while a decrease in sodium occurred in 83 per cent (91/110) averaging 3.1 mEq. per L. In any one animal, the magnitude of the sodium and potassium shifts appeared unrelated. The movement of cations was evident within 5 minutes after injection of the first increment of acetylstrophanthidin.

The amount of drug required to produce ventricular tachycardia was unrelated to the control serum levels of sodium, potassium, or calcium; however, animals requiring the most digitalis manifested the greatest cation shifts. When digitalization was carried to ventricular fibrillation, the rise in potassium averaged 1.8 mEq. per L., while the fall in sodium was 11.3 mEq. per L.

Administered potassium may protect against digitalis induced arrhythmias; however, when potassium is infused in amounts insufficient to cause severe hyperkalemia, cardiac standstill may ensue after relatively small doses of digitalis are given simultaneously. This is probably due to potassium intoxication rather than digitalis overdosage for the following reasons: 1. Cardiac standstill does not occur after larger doses of acetylstrophanthidin when potassium is not supplemented. 2. The serum potassium concentration rises percipitously after digitalis is given. 3. The electrocardiogram records the evolution of hyperkalemia rather than ventricular arrhythmias. 4. The lethal process is reversible by potassium-lowering procedures.

Digitalis blocks the entry of potassium into cells. When potassium is administered, an arteriovenous gradient is demonstrable across skeletal muscle, portal bed and the liver, denoting potassium uptake. Simultaneous digitalization abolishes these gradients.

Patients with advanced heart disease may develop severe and terminal hyperkalemia resulting from similar digitalis induced potassium shifts.

Physiologic Definition of Pulmonary Vascular Status in Atrial Septal Defect

Peter C. Luchsinger, Kenneth M. Moser, Washington, D. C., and Albert Buhlmann, Zurich, Switzerland.

The oxygen saturation of pulmonary venous blood was determined in 6 patients with atrial septal defect in whom pulmonary hypertension was present at rest or during exercise.

One patient demonstrated both normal pulmonary artery pressure and pulmonary venous saturation at rest. However, during exercise pulmonary hypertension and pulmonary venous desaturation developed, while pulmonary vascular resistance was unaltered. Two patients had high pulmonary resistance, pulmonary hypertension and pulmonary venous desaturation at rest. Exercise in 1 of these patients produced an increase in both pulmonary hypertension and pulmonary venous desaturation, while the high pulmonary resistance was maintained. Three patients, studied only at rest, demonstrated pulmonary hypertension, but normal pulmonary venous desaturation in the face of a high pulmonary resistance.

The importance of pulmonary vascular changes in the preoperative evaluation of patients with congenital heart disease has been widely recognized. The variable pattern of such changes has been indicated by pathologic studies (Edwards). There has been need, therefore, for diagnostic technics which can define the pulmonary vascular status before surgery.

Previous studies in a variety of disorders in which pulmonary vasculature is severely compromised have demonstrated that such changes are reflected physiologically by fixation of pulmonary resistance, pulmonary hypertension and pulmonary venous desaturation. Such concepts are equally applicable to patients with congenital heart disease. Therefore, those patients described in whom both pulmonary hypertension and pulmonary venous desaturation existed at rest, fall into the category of most severe pulmonary vascular compromise. The patient who developed these abnormalities only with exercise represents a less severe restriction of pulmonary vascular bed. Those patients in whom normal pulmonary venous saturation exists in the face of pulmonary hypertension at rest, can be identified as individuals without sufficient pulmonary capillary loss to become manifest at resting levels of pulmonary blood flow.

Intracardiac Phonocardiography in Left Heart Catheterization

Aldo A. Luisada and Chi K. Liu, Chicago, Ill.

A new method for intracardiac phonocardiography is based on the use of a high-frequency strain gage, a different circuit, and a set of filters, in connection with a cathode-ray oscilloscope with graphic recording. With this system, sonic vibrations of the blood are transmitted through a polyethylene catheter to the membrane of the gage, selected and recorded. This method was used in the course of left heart and aortic catheterization in 20 cases with mitral or aortic lesions.

These studies have proven that the heart sounds become larger by approaching the mitral valve; so does the systolic murmur caused by mitral regurgitation. Its vibrations are well recorded and of diagnostic value. The diastolic murmur of mitral stenosis can be recorded in the left atrium, but is

much larger in the left ventricle. The same applies to the opening snap of the mitral valve. The first sound presents a remarkable delay in comparison with normal subjects. Murmurs of aortic stenosis and insufficiency can be recorded either in the left ventricle or in the ascending aorta (catheterization of brachial artery).

Production of Experimental Myocardial Failure by Coronary Artery Embolization

Emanuel Marcus, Louis N. Katz, Ruth Pick, and Jeremiah Stamler,† Chicago, Ill.

We have attempted to simulate chronic coronary insufficiency in the dog, to be used as a test object for myocardial revascularization procedures. Our method has been, with modifications, that of Munro, Owens, Balchum and Swan; this involves embolization of the coronary arteries with inert divinyl benzine spheres of measured size. Acute coronary insufficiency is easily produced; chronic coronary insufficiency, including evidence that it exists, is more difficult to attain.

Evidence is presented (with electrocardiographic tracings, gross photographs and photomicrographs) to show that the technic employed can produce: (1) diffuse myocardial scarring, (2) myocardial infarcts, and (3) coronary arteriosclerosis. It is shown further that such lesions may exist days, weeks, and many months, defying detection by electrocardiographic tracings that show only transient, little, or no deviations from normal. In the extreme, we have produced the familiar picture of congestive heart failure with ascites, pleural effusion, and elevated venous pressure. The development of these findings following experimental creation of valvular defects, such as tricuspid insufficiency, is well known. The creation of congestive cardiac failure on the basis of myocardial failure simulating chronic coronary insufficiency of the human, however, has not yet been reported to our knowledge. Many uses exist for such an experimental test object.

Differentiation of Mitral Stenosis and Mitral Regurgitation By Means of Left Atrial Pulse Contours

Hiram W. Marshall, Daniel C. Connolly, and Earl H. Wood, Rochester, Minn.

The left atrial pulse contours of 43 patients with mitral valve lesions undergoing left heart catheterization in whom simultaneous left atrial, left ventricular, and aortic pressures were obtained were analyzed in an attempt to find a method that would differentiate mitral stenosis from regurgitation. The end diastolic pressure gradient across the mitral valve in patients with predominant regurgitation was in the same range as in those with predominant stenosis, and in many patients higher than in those with pure mitral stenosis. Previously suggested methods for differentiation of stenosis from regurgitation by left atrial pulses were studied, including the rate of descent of the V wave (Ry descent), the V minus Z, V minus C, V minus B and V minus mean left atrial pressure. A correlation was demonstrated between these parameters and the degree of insufficiency determined at operation, but complete separation of patients with predominant stenosis and regurgitation was not attained. A positive correlation was demonstrable between the above parameters and mean left atrial pressure ($\overline{P}_{LA}$); consequently discrimination was improved by utilizing ratios calculated by dividing by the mean pressure. The ratios $V/\overline{P}_{LA}$ and $Ry/\overline{P}_{LA}$ gave the better discrimination. Overlap persisted, however, in 3 and 5 patients respectively. Other parameters studied, including the time relationships of the V wave to ventricular systole, could not be correlated with the degree of regurgitation. Attempts to improve discrimination by multiple variable analysis were not successful. Complete differentiation of predominant stenosis from regurgitation on the basis of left ventricular and atrial pressures alone seems therefore impossible. Analysis of such pulses is, however, of diagnostic value, particularly the relation of the peak V wave to mean left atrial pressure.

Blood Pressure in White People Over 65

Arthur M. Master, Richard P. Lasser, and Harry L. Jaffe, New York, N. Y.

Blood pressure in old age is of great importance because of the currently large number of people 65 and older (15,000,000) and because over 75 per cent of persons now 40 will live to at least 65. This study consists of 5,757 apparently healthy, ambulatory white persons 65 to 106 years old. This group was geographically distributed throughout the United States in proportion to the total aged population. It was internally homogeneous, and the curves of frequency distribution were typically bell-shaped.

Mean and modal pressures, standard deviations and frequency distribution curves were calculated for each sex both by 5-year age groups and for the entire group. Systolic pressure did not continue to rise with age after 70 to 74, nor diastolic after 65. Mean pressure for all males was 145/82 and for females was 156/84. Modal pressure was 140/80 for both sexes. Females manifested higher systolic pressures at all ages but closely approached males after age 95. Since the variation of pressure with age was slight, 2 ranges were computed for all persons 65 and over for each sex: 1. The middle 80 per cent ($\pm 1.282\sigma$) for males was $\frac{115\text{–}175}{70\text{–}95}$, and for females $\frac{120\text{–}192}{65\text{–}102}$. Pressures within these limits,

if not associated with evidence of hypertensive heart disease, do not require antihypertensive therapy. 2. The middle 95 per cent ($\pm 2\sigma$) for males was $\frac{100\text{–}190}{62\text{–}102}$, and for females $\frac{100\text{–}212}{55\text{–}112}$. Pressures beyond these limits are definitely abnormal.

Acute Effect of Mecamylamine on the Hemodynamic Changes in Dogs

Henry Page Mauck, Jr., Jack Freund, and Reno R. Porter, Richmond, Va.

The acute hemodynamic effects of mecamylamine were studied in 14 healthy mongrel dogs. The animals were anesthetized with chlorolose and urethane and cardiac catheters positioned in the pulmonary capillary, pulmonary artery, right ventricle and right atrium. Cannulas were inserted in the carotid and femoral arteries. Pressure recordings were made simultaneously from all positions and cardiac output was measured by an indicator dilution method (T-1824).

After the dogs had become basal under anesthesia control pressures, cardiac output and blood volumes were obtained. Mecamylamine 0.5 Gm. per Kg. was then injected into the right atrial catheter. Pressures were obtained at 1, 5, 10 and 30 minutes from the 4 cardiac catheters and carotid artery. Cardiac outputs were obtained at 10 and 30 minutes following drug injection.

A decrease was noted in cardiac indices, and systolic, diastolic and mean carotid arterial pressure at 1, 5, 10 and 30 minutes. These differences were statistically significant. The right atrial pressure was significantly decreased only at the 5-minute determination and this was due to a fall in diastolic pressure. Right ventricular pressures fell significantly, due predominantly to a fall in the systolic component. No significant changes were noted in systemic and pulmonary vascular resistance.

In summary, with mecamylamine injection in dogs, a fall in cardiac indices and carotid pressures were noted without any significant change in either systemic or pulmonary resistance.

Fulminating and Fatal Aortic Insufficiency Due to Nonspecific Aortitis

Johnson McGuire, Edward A. Gall, and Ralph C. Scott, Cincinnati, Ohio.

During the past few years we have had the opportunity to observe 3 young women patients with wide open aortic insufficiency terminating fatally. There was no history of syphilis, rheumatic fever, congenital heart disease, or rheumatoid arthritis. None had the stigmata of Marfan's syndrome. Blood cultures, serologic studies for syphilis, antistreptolysin titers were negative. Treponema pallidum immobilization tests were not done.

At autopsy each case showed a peculiar lesion in the ascending aorta and arch consisting of marked intimal thickening and wrinkling. There was dilatation of the aortic valve ring. Microscopically, there was extensive mural alteration with destruction of the media. It is our opinion that this represents a chronic nonspecific aortitis of unknown etiology.

Cardiovascular Aspects of the Ehlers-Danlos Syndrome, an Heritable Disorder of Connective Tissue

Victor A. McKusick and Richard S. Ross, Baltimore, Md.

Single instances of tetralogy of Fallot and atrial septal defect in association with Ehlers-Danlos syndrome (E-D) and two cases of dissecting aneurysm of the aorta in persons with stigmata of E-D have been reported. Acrocyanosis was impressive in some series.

Two new cases of E-D with unusual cardiac manifestations are described: (1) An 18-year-old female, of short stature, has hyperextensible skin and joints, posterior dislocation of the elbows, deformity of the pinnae, "flabbiness" in early years of life, delay in sitting and walking, and "glove-and-moccasin skin" of feet and hands; (2) a 40-year-old male has hyperextensible skin and joints, redundancy of the colon, duodenal diverticula, flat feet, genu recurvatum, redundant skin of the eyelids, repeated rectal prolapse, and "glove-and-moccasin skin." Both cases are apparently sporadic. In neither is cutaneous fragility and bruisability impressive.

Case 1. Murmur and cardiomegaly were discovered at 15 months. Palpitations are the main symptom. Examination reveals bizarre systolic and diastolic murmurs, with a superficial quality at times suggesting friction rub. Anomalous mitral valve, possibly of Ebstein type, is suspected.

Case 2. Was always rejected for armed service and insurance because of a murmur present from birth. At age 39 congestive failure developed. At age 40, the findings included massive cardiomegaly, B.P. 100/70 mm. Hg grade III systolic murmur in the aortic area transmitted to the neck, grade II higher pitched murmur at the apex, and a faint decrescendo diastolic at the left sternal border. Right heart catheterization showed no shunt, great cardiomegaly, pressure of 56/2/5 mm. Hg (right ventricle). Abnormalities of the mitral and aortic valves are thought to be present.

In E-D there appears to be a loose organization of the collagen wickerwork. The valves, chordae tendineae and fibrous skeleton of the heart might be expected to be abnormal. The mitral insufficiency thought to be present in the 2 patients reported could be explained on this basis. Eventually cardiovascular changes in E-D will probably be found to fit into as precise a pattern as those of Marfan's syndrome.

Work of Digital Vasoconstriction Produced by Infused Norepinephrine in Primary Hypertension

Milton Mendlowitz and Nosrat N. Naftchi, New York, N. Y.

Pressure and flow were measured in the digital circulation after vasodilatation by indirect heating for one-half an hour or more supplemented by the intravenous administration of 0.8 mg. per Kg. of either pentamethyl, diethyl-3 aza pentone-1,5 diammonium dibromide or 2,6 dimethyl-1,1-diethyl piperidinium bromide (autonomic ganglion blocking drugs) and during continued indirect heating and the intravenous infusion with a pump of additional ganglion blocking drug and norepinephrine sufficient to raise the blood pressure to, or somewhat above, its initial level as determined with the subject recumbent and at rest. The radius equivalent of the digital blood vessels during both phases of the procedure was then calculated by applying Poiseuille's law to the flow-pressure data. Flow was measured calorimetrically and systolic and diastolic pressures were measured with a Gaertner capsule by the "flushing" technic and the point of cessation of throbbing respectively. The mean pressure was considered to be diastolic pressure plus one-third of the pulse pressure. To obtain effective mean pressure, a calculated venous pressure, and pressure axis intercept correction were subtracted from the mean pressure. The radius equivalents were calculated from flows and effective mean pressures, the length factor being assumed to be constant. From these radius equivalents and blood pressures, the work of vasoconstriction in ergs per milligram of norepinephrine infused per minute was calculated.

Significantly greater digital vasoconstrictive work was elicited per milligram of norepinephrine infused per minute in 15 patients with primary hypertension than in 15 normotensive subjects. Since there was no overlapping of the results in the 2 groups, it is possible that the procedure may be useful in detecting early or masked primary hypertension.

Posteromedial Annuloplasty: Correction of Acquired Mitral Insufficiency under Direct Vision Utilizing a Pump-Oxygenator

K. Alvin Merendino, John E. Jesseph, Paul W. Herron, George I. Thomas, and Roy R. Vetto, Seattle, Wash.

The abnormal hemodynamic and anatomic changes which accompany acquired mitral insufficiency are fairly well understood. Anatomically, the annulus has become enlarged and "dislocated" cephalad into the left atrium. The progression of the latter enhances regurgitation by effecting elevation of the annulus to which the valve properly is attached, thereby pulling more taut the chordae tendineae. As this occurs, the movement of the anterior and posterior cusps is limited and regurgitation is enhanced.

In approximately 100 cases of mitral stenosis, 45 per cent had associated mitral insufficiency. In most it was minor; however, in a few it was thought to represent the primary lesions. In practically all instances, the regurgitant jet was toward the posteromedial area of the valve orifice. Therefore, attention to the correction of regurgitation has centered about this area.

By suturing the anterior and posterior aspects of the annulus posteromedially, the size of the annulus is decreased, thereby decreasing the valve orifice. In addition, theoretically, the valve is inverted, thereby slackening the tension on the chordae tendineae and thus "lengthening" them. As a result, the valves have less distance to travel and greater mobility to effect the closure of the orifice during ventricular systole.

Five patients with rheumatic fever thought to have predominant mitral insufficiency were operated upon under direct vision utilizing a pump-oxygenator. One patient had the combined lesions of aortic insufficiency and mitral regurgitation; another patient had 4-chamber failure with mitral stenosis and regurgitation. The experiences gained with these 2 patients will be documented. Three patients had "pure mitral insufficiency." All were corrected by posteromedial annuloplasty. Pressure measurements in the left atrium indicated complete correction of the regurgitation. Preoperative apical systolic murmur grade III to V disappeared postoperatively. All patients recovered from perfusion. One was lost in the early postoperative period. The other 2 patients have been strikingly improved.

Prevention of Cholesterol Deposition in the Rabbit Aorta by Oral Nicotinic Acid

Joseph M. Merrill and Janet Lemley-Stone, Nashville, Tenn.

Previous work has shown that hypercholesterolemia may be reduced by oral nicotinic acid. To determine if nicotinic acid will prevent deposition of cholesterol in arteries, groups of rabbits were fed rabbit chow (group I); rabbit chow plus 2 per cent cholesterol (group II); and rabbit chow plus 2 per cent cholesterol with 0.4 per cent nicotinic acid (group III). Serum cholesterol was determined weekly. At the end of 8 weeks the animals were sacrificed and tissue samples from the aorta and liver were examined microscopically. Total tissue cholesterol was measured by the Kingsley and Schaffert procedure. The following average values were found. Serum: group I, 48 mg. per cent; group II, 1262 mg. per cent; group III, 509 mg. per cent. Aorta: group I, 133 mg. per cent; group II, 381

mg. per cent; group III, 138 mg. per cent. Livers: group I, 282 mg. per cent; group II, 6553 mg. per cent; group III, 1506 mg. per cent. The aortas of rabbits fed 2 per cent cholesterol without nicotinic acid had approximately 3 times as much cholesterol as the controls, while aortas from the group with added nicotinic acid contained no more cholesterol than the aortas from the control group. The difference in the cholesterol content of the aortas from group II and III was highly significant ($p < 0.001$). Rabbits fed 2 per cent cholesterol had higher levels of cholesterol in the liver than did the control animals. The animals with added nicotinic acid had only one fourth as much liver cholesterol as group II ($p < 0.02$).

In these experiments the addition of nicotinic acid to a diet high in cholesterol was not only effective in lowering serum cholesterol but prevented cholesterol deposition in the aorta.

Early Postoperative Results Following Partial Correction of Transposition of the Great Vessels

Robert A. Miller and Thomas G. Baffes, Chicago, Ill.

A clinical study of 20 patients surviving a partial correction of transposition of the great vessels will be presented. The procedure done in these patients has been previously described by one of the authors and consists of transplantation of the inferior vena cava to the left atrium, utilizing a homologous aortic graft, and simultaneous transplantation of the right pulmonary veins to the right atrium. This procedure accomplishes redirection of approximately 60 per cent of the patient's circulation.

The clinical examination, roentgenographic study, electrocardiograms, peripheral arterial oxygen saturation and other data will be presented. The studies cover periods from 6 months to over 2 years following the operation. It is believed that this series represents the largest group of postoperative survivors in children with transposition of the great vessels reported to date.

An additional 4 cases which represent late postoperative deaths, i.e., those occurring after discharge from the hospital, will be discussed.

The data tend to show that, if the child survives the immediate postoperative period, a striking improvement is noted. In no instance has a child survived to have slight improvement only.

Nature of Hypoxia and Therapeutic Role of Intermittent Inspiratory Positive Pressure Oxygen Breathing in Acute Diffuse Pulmonary Lesions, Including Pulmonary Edema

William F. Miller, James P. Lillehei, Brian J. Sproule, and Carleton B. Chapman, Dallas, Tex.

Hypoxia, considered the result of a diffusion defect, has been accepted as the principal cause of dyspnea in most patients with acute diffuse pulmonary lesions, including pulmonary edema. Thus, pure oxygen breathing should relieve the dyspnea and the hypoxia. However, more rapid clinical improvement noted with the use of intermittent positive pressure oxygen breathing (IPPB/I-O_2) as compared to pure oxygen without pressure prompted the present investigation.

Thirty-one patients were subjected to gas exchange and, in some instances, hemodynamic studies. PaO_2 was measured by the Clark polarographic electrode. All patients revealed hypoxia on ambient air breathing, PaO_2 20–65 mm. Hg, average 45; $PaCO_2$ ranged 24–68 mm. Hg, average 43, and the A-a pO_2 ranged 30–82 mm. Hg, average 58. Dyspnea was prominent in every case and hypotension or shock was not infrequent. On pure oxygen breathing, values were: SaO_2 80–100 per cent, average 90; PaO_2 46–490, average 144; and A-a pO_2 173–647, average 538. In every case, PaO_2 increased on IPPB/I-O_2 breathing (without bronchodilator), 80–583 average 323. A-a pO_2 accordingly decreased, average 346 mm. Hg. Even when hypoxia was corrected by oxygen breathing without pressure, dyspnea and hypotension usually persisted until oxygen was administered by IPPB/I.

In 5 patients with severe pulmonary edema, IPPB/I-O_2 resulted in significant lowering of the mean venous pressure and slight to marked increase in the arterial pressure. In 4 patients with shock and pulmonary edema following acute myocardial infarction, arterial pressure returned to normal levels only after IPPB/I-O_2. The relationships of hemodynamic changes to cardiac output as well as alterations in pulmonary compliance and resistance are being studied.

The principal effects of IPPB/I-O_2 are to correct the principal cause of dyspnea by decreasing the work of breathing and to improve the distribution of ventilation and thus effect better oxygenation, and increased lymphatic reabsorption of edema fluid. The principal mechanisms of hypoxia are disturbed ventilation-perfusion relationships, and arteriovenous shunting in the lungs.

Abnormalities of Blood Distribution in Congestive Heart Failure

William R. Milnor and Lucien A. Campeau, Baltimore, Md.

To explore the hypothesis that congestive heart failure is associated with redistribution of blood within the cardiovascular system, separate determinations of the blood volume of the heart, lungs, systemic veins, and remainder of the vascular system were made in 7 patients with arteriosclerotic or rheumatic heart disease. Measurements were made while signs of combined right and left ventricular failure were present and were repeated after cardiac

compensation had been restored by 2 to 3 weeks of hospital treatment.

Plasma volume was measured with I^{131}-labeled serum albumin, erythrocyte volume with Cr^{51}, diastolic heart volume by timed biplane radiography, and cardiac output by the dilution method. Mean transit times from arm vein to brachial artery and arm vein to right heart (using an external collimated scintillation counter) were measured and used to calculate "venous" and "cardiopulmonary" blood volumes by the Hamilton formula.

In congestive heart failure, the mean total blood volume (39.3 ml. per cm. height), venous blood volume (10.2 ml. per cm.), and cardiopulmonary blood volume (9.3 ml. per cm.) were all significantly above the range observed in normal subjects. With treatment, mean total blood volume decreased to 29.3 ml. per cm. (within normal limits); cardiac output increased, but mean transit times shortened almost proportionately, so that calculated venous and cardiopulmonary blood volumes decreased only slightly, remaining above normal limits in 5 patients.

We tentatively conclude that: 1. The increase in total blood volume that usually occurs with heart failure is shared by all major segments of the cardiovascular tree. 2. Treatment by conventional methods brings about a decrease in total blood volume, principally due to a decrease in the blood volume of the small systemic vessels. 3. In some patients an increased venous blood volume persists after cardiac compensation is restored although venous pressure returns to normal, implying decreased venous tone.

Atrial Fibrillation as a Self-Sustaining Arrhythmia Independent of Focal Discharge

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According to the currently popular unitary theory, it is assumed that atrial tachycardia, flutter, and fibrillation are due to the repetitive discharge of one or more ectopic foci. It is implied that the arrhythmia persists as long as the focus continues to fire and ceases when the focus is arrested. It is possible, however, that such a focus (as induced by local application of aconitine) may set up a self-sustaining rhythm which maintains itself after the initiating focus has been blocked out or suppressed. To test this hypothesis, "ectopic foci" were set up by electric stimulation or by injection of aconitine into the tip of the right atrial appendage in dogs under barbiturate anesthesia. Vagi were cut. Repetitive stimulation of the atrium at a frequency of 20 c.p.s. or more produced fibrillation which stopped at once or within a few seconds after cessation of stimulation. During right vagal stimulation, repetitive excitation of the atrium caused fibrillation which persisted after termination of atrial stimulation (arrest of the "focus") for as long as vagal stimulation was continued. Atrial fibrillation resulting from aconitine injection terminated promptly when the base of the atrium was firmly compressed but persisted in spite of clamping when the vagus was stimulated. Flutter (at a frequency of 7 per second or less) induced by aconitine terminated promptly upon clamping the base of the atrium whether or not the vagus was stimulated. The results are consistent with the hypothesis that atrial fibrillation is a self-sustaining arrhythmia which may be initiated by an ectopic focus but is not dependent upon the continuing activity of such a focus for its survival.

Transbronchial Left Heart Catheterization: Improved Technic and New Applications in Clinical Research

Andrew G. Morrow, Eugene Braunwald, and Herbert L. Tanenbaum, Bethesda, Md.

Two methods of left heart catheterization are commonly employed in this country, the percutaneous and the transbronchial. The chief advantage of the transbronchial route is its safety, proved in a series of more than 500 catheterizations performed in this clinic without mortality or significant morbidity. The application of the transbronchial method in hemodynamic investigation has been limited, however, by inability to determine cardiac output and to make prolonged observations with the patient in a steady basal state. These limitations have been obviated by recent modifications in technic. After the measurement of left heart pressures, cardiac output is determined by the injection of indicator dye into the left ventricle. The transbronchial needle is then withdrawn while the catheter remains in situ. For simultaneous measurements of left atrial and left ventricular pressures, a second transbronchial puncture is performed. The bronchoscope and needle are then removed. Determinations of ventilation, oxygen consumption and the respiratory quotients indicate that patients return to a steady basal state within 15 to 20 minutes after bronchoscopy. Measurements of left heart pressures and cardiac output are then continued for prolonged periods. The effects of various drugs and of exercise with a bicycle ergometer on left heart pressures can be determined.

The transbronchial method appears preferable to the percutaneous as it combines the advantages of safety and the ability to make extended observations with the patient in a known physiologic state.

Critical Evaluation of the Equivalent Cardiac Dipole Concept

Ralph F. Morton and Daniel A. Brody, Memphis, Tenn.

Recent reports from other laboratories indicate that the heart is electrically equivalent to a single,

fixed-location, current dipole immersed in an electrically homogeneous volume conductor. Because such behavior implies a number of important theoretical and practical consequences, we reexamined the applicability of the equivalent cardiac dipole concept to clinical electrocardiography. In essence the study consisted of the analysis of electrocardiographic mirror patterns by means of an advanced cancellation technic. The superiority of our method was due to a novel electromechanical computer, used in conjunction with a high-fidelity electrocardiograph, which permitted analysis of electrocardiographic mirror pairs on an *instant-by-instant* basis, as well as the usual peak-to-peak basis.

Fifty-eight cancellations of the QRS complex were painstakingly performed on 25 normal subjects. On a peak-to-peak basis, 34 (58.6 per cent) of the cancellations were excellent, 12 (20.7 per cent) were good, 6 (10.4 per cent) were fair, 4 (6.9 per cent) were poor, and 2 (3.4 per cent) were bad. The distribution of 330 *instantaneous* cancellations, determined from the same group of records, was 140 (42.4 per cent) excellent, 37 (11.2 per cent) good, 27 (8.2 per cent) fair, 28 (8.5 per cent) poor, 57 (17.3 per cent) bad, and 41 (12.4 per cent) "no cancellation." Thus, in almost one third of the instantaneous determinations, cancellation did not occur or was extremely poor. These highly inferior values were distributed rather uniformly throughout the QRS cycle.

The present study confirms our earlier prediction that peak-to-peak cancellations are misleading indicators of dipolar activity, especially because any electrocardiographic complex can be completely canceled at least twice during its cycle. Further analysis shows that excellent cancellation does not necessarily require a manifestly dipolar distribution of the electromotive forces of the heart. Actually, certain nondipolar distributions were shown to produce better cancellation than corresponding dipolar distributions.

Intracardiac Phonocardiography: Correlative Study of Mechanical, Acoustic and Electric Events in Experimental Valve Lesions

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Temporal relationships between pressure events and heart sounds or murmurs may be more accurately assessed when these measurements are made at their site of origin. Classical correlation studies have been based largely on indirect pulses and sounds recorded at a distance from their source.

Intracardiac heart sounds and pressures were recorded simultaneously by passing a double lumen microphone catheter, utilizing a Glennite pickup, into the cardiac chambers of either side of the heart in 60 dogs. Pressure pulses transmitted through the hollow lumen of the catheter monitored the position of the microphone. Additional pressures were obtained by needle puncture of other cardiac chambers.

During experimental aortic or pulmonic stenosis, diamond-shaped ejection murmurs were recorded from the corresponding great vessel, indicating that this characteristic shape of the murmur is generated at the stenotic area and does not depend on transmission through the chest wall for its configuration. The diastolic murmur of aortic insufficiency, which began 0.02 second before the incisura, unexpectedly became louder when aortic stenosis was superimposed. Possibly this is due to increased turbulence of flow created when the regurgitant stream traversed the narrowed aortic valve area. When mitral stenosis was superimposed on mitral insufficiency, the systolic regurgitant murmur recorded in the left atrium did not disappear until a high left atrioventricular filling pressure gradient appeared.

Systolic flow murmurs, apparently dependent on increased volume and velocity of blood flow, could be recorded in the great vessels, accompanying the first normal contraction after frustrated premature beats. The sudden augmentation of flow during the first beat following the release of pulmonic or aortic stenosis produced a systolic murmur in the great vessels. That these flow murmurs need not depend on relative disproportion between adjacent chambers was indicated by the fact that no differential pressure gradient was demonstrable between the ventricle and great vessel at the time these murmurs occurred.

Biochemical Analysis of the Myocardium in Experimental Hypothermia

Peter V. Moulder, Lillian Eichelberger, and Michael Roma, Chicago, Ill.

Biochemical studies on the blood, serum and myocardium of normal dogs have revealed only moderate changes during the puppy life span (comparisons between 87 to 124 days and 142 to 218 days). In considering a kilogram of heart muscle with aging, there is an increase in the cell mass from 679 to 714 Gm. with a stable cell water percentage of 75 per cent and 76 per cent. There is a decrease in the ultrafiltrate volume from 290 to 253 Gm. with the connective tissue solids remaining stationary. Cellular concentration of potassium was 108 mEq. per Kg., of magnesium 22 to 23 mEq. per Kg.; cell water concentration of potassium was 142 mEq. per Kg., and of magnesium 30 to 31 mEq. per Kg. Subtracting the calcium calculated to be in the extracellular fluid mass from the total muscle calcium revealed only 1 to 1.2 mEq. per Kg for the connective solids and the cell (referred to as Δ calcium). Using a generally older age group of puppies, total body hypothermia was induced by

ce water immersion, using light ether anesthesia nd autorespiration. After a 20- to 30-minute period t 22 to 25 C. blood was sampled and the heart apidly removed for analysis. Raw data showed indings similar to the older age group of normal logs but with these exceptions: the total myocardial odium content was exactly that of the younger normal group, 34 mEq. per Kg.; the serum potas- ium was low compared to the normal pups as well as to the precooling levels in the experimental animals, 3.13 mEq. per Kg. vs. approximately 4.5 mEq. per Kg.; a lowered muscle potassium re- flected this serum level in its ultrafiltrate. Cal- culated phase mass data in the tissues from the 8 experimental animals revealed patterns similar to those of the older age group of puppies; extra- cellular water of 250 Gm., connective tissue solids of 35 Gm., cell water of 548 Gm., and cell solids of 167 Gm. for a kilogram of myocardium. Cell water percentage was 77 per cent. Cellular concentration of potassium was 113 mEq. per Kg.; cell water concentration was 147 mEq. per Kg. The other major cellular cation, magnesium, showed more deviation in the hypothermia group than in the normal. Final concentrations averaged 23 mEq. mg. per Kg. cells, and 29 mEq. mg. per Kg. cell water. The $\triangle$ calcium as described above was 1.12 mEq. per Kg.

Therefore, under the circumstances of autores- piration and light ether anesthesia, the canine myocardium removed during experimentally in- duced hypothermia of 22 to 25 C. shows no signifi- cant deviation from the normal in its electrolyte pattern, phase masses, and concentrations of major cellular cations.

Osseous Venography: Aid to Differential Diagnosis of Peripheral Vascular Diseases

Isidor Mufson, New York, N. Y.

A technic which visualizes the deep venous systems of the ankle and leg by the introduction of iodinated compounds into the bone marrow was first described by Begg. Its use has been found in- valuable when difficulty is encountered in dif- ferentiating between venous and nonvenous dis- turbances which clinically simulate each other.

Method. A needle with its distal 1½ inch threaded and its stylet secured by a Luer-Lok syringe is introduced and screwed through the cortex of the calcaneus or 1 of the malleoli of the ankle. Ten milliliters of Hypaque or Urokon is introduced rapidly, and x-rays of the leg are taken immedi- ately, 1 and 2 minutes later, in AP venae comites— posterior tibial, anterior tibial and peroneal—their intercommunicating veins, the popliteal and super- ficial femoral veins, and their valves are visualized. When valves are incompetent, the perforator veins and both the saphenous veins are visualized. Tor- tuosity indicates deep varicosities and absence of normally placed veins, and venous obstruction because of fresh or old phlebitis.

These x-ray findings, and their interpretation, were especially valuable in local edema states where there are no visual varicosities or palpable cord- like veins. We used the technic when pain and swelling of the ankle suggested either local phlebitis, or a fibro-osseous disease for which the laboratory and the ordinary x-ray film gave no information. Edema makes the superficial veins inaccessible to venipuncture and cutdown. Ascribing edema to lymphatic obstruction of the deep venous system must first be ruled out. Differential diagnosis be- tween a tear of the soleus muscle and deep phlebitis is often difficult; both have local tenderness, swell- ing, and a positive Homan sign. When ruptured muscle fibers ooze, anticoagulants certainly will ag- gravate the situation. It is apparent that osseous venography is most important.

Visualization of incompetent and varicosed perforator veins is necessary, not only for the diagnosis, but as an aid to the surgeon who is enabled to tie the perforator veins more effectively. This should improve results.

Functional and Morphologic Changes in the Heart-Lung Preparation Following Administration of Adrenal Hormones

Gabriel G. Nahas, Washington, D. C., Joel G. Brunson, and William M. King, Minneapolis, Minn.

The production of cardiac lesions in intact dogs after a single injection of 5 to 20 μg. per Kg. of epinephrine or norepinephrine was reported earlier. It was also observed that such lesions were more extensive if the animal had been pretreated with hydrocortisone. The present series of experiments was performed to study the effect of these hormones on the denervated heart.

Thirty heart-lung preparations were completed, using mongrel dogs of similar age and weight. Total weight of the preparation was 2 Kg. Cardiac out- put, outflow pressure, and electrocardiogram were continuously recorded. Seventy minutes after completion of the preparation, inflow was clamped and the heart was rapidly excised. Eight prepara- tions were used as controls, 7 were given 4 μg. of epinephrine or norepinephrine per minute for 5 minutes. Seven other preparations received 5 mg. of hydrocortisone in a single injection, and 8 were given hydrocortisone followed 10 minutes later by epinephrine or norepinephrine. In the control series, cardiac work, output, and rate fell slightly and gradually in the course of the 70-minute experi- ments. No macroscopic or microscopic alterations were observed after removal of these hearts, except in the immediate vicinity of the intracardiac caval cannulas.

The infusion of sympathomimetic amines caused

a marked rise in cardiac work and rate which dropped below their control values after cessation of the infusion; these changes were more pronounced when the preparation was pretreated with hydrocortisone. Hydrocortisone alone did not modify significantly any of these variables. However, all the hearts receiving one of the adrenal hormones presented extensive lesions of the myocardium, valves, and coronary vessels; these lesions were more severe in the hearts in which both adrenal hormones were used.

Prompt Use of Anticoagulants in Impending Myocardial Infarction

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Impending or threatened myocardial infarction is manifested by definitely worsening anginal pain over a span of hours, days, or weeks, or by development of a new constellation of "coronary" symptoms not explained by extracoronary trigger factors and not associated with signs of fresh infarction. At the bedside, any distinction from syndromes of "acute coronary insufficiency," "coronary failure," or "intermediate coronary syndrome," is artificial as the precise phase of coronary atherosclerosis being manifested can be pin-pointed only in retrospect.

We have treated 313 private patients in the past 10 years presenting premonitory signs of myocardial infarction: of 248 men and 65 women, aged 40 to 80 years, 202 (65 per cent) had at least 1 previous myocardial infarction. Heparin was used for 1 week or longer, followed by oral anticoagulants. Restricted activity, vasodilators, reassurance, and sedatives were used routinely.

Relief of pain was strikingly coincident with full heparinization. Only 20 (6.3 per cent) developed frank myocardial infarction; 5 died within 30 days, 1 within 60 days. Examples of failures will be detailed. Electrocardiographic signs of slight myocardial necrosis with or without increase in sedimentation rate and leukocytes were present initially or developed in 155 patients. Of 293 cases not developing frank infarction, none died within 60 days (short term) while using anticoagulants. Of 27 patients abandoning anticoagulants before 60 days, 16 (60 per cent) developed frank infarction during the next 60 days with 4 survivals. Hemorrhage occurred in 15 per cent (no deaths) and was readily controlled. Anticoagulant treatment was continued indefinitely in 281 cases; long-term results will be discussed briefly.

No control group has been compiled. How many without anticoagulants would develop frank infarction, one cannot say as there are no studies recorded.

Since only 6.3 per cent of 313 patients developed frank myocardial infarction, we believe this reflects a definite protection afforded by prompt heparin therapy.

Effect of Certain Unsaturated Fatty Acids on Serum Lipids

Martin M. Nothman, Lowell Bellin, and Samuel Proger, Boston, Mass.

Studies on the effect of unsaturated fatty acids on serum lipids have been performed on 21 patients. All had hypercholesterolemia with or without hyperlipemia. They were fed a stable mixture of the essential fatty acids consisting of 49 per cent linoleic acid, 49 per cent linolenic acid and 2 per cent arachidonic acid. The amount given was 25 ml. daily. There were no dietary restrictions. Changes in serum lipids following administration of these fats have been studied.

In general, the effect of the unsaturated fatty acids was about the same in all subjects examined. Results have been as follows: 1. Within the first month there was a fall in the amount of total lipids. The drop was greater in those cases where the initial values were high but it was also definite where the total amount of lipids was normal or slightly elevated. There was also always a marked decrease in the amount of fatty acids. 2. The serum cholesterol decreased regularly, generally more in the second month of the ingestion of the unsaturated fatty acids progressing with continued administration. The cholesterol esters appear to decrease proportionately more than the free cholesterol. 3. There was no definite pattern as to the effect of the unsaturated fatty acids on phospholipids. In some patients the values fell, particularly in those with high figures in the beginning; in others, there was even a slight increase. 4. The ratio of cholesterol to phospholipids was greater than 1 in all cases ranging from 1.04 to 3.67. It decreased without exception after administration of the unsaturated fatty acids. In 7 cases the ratio decreased to less than 1.

This mixture of essential fatty acids appears to be effective in lowering serum cholesterol and perhaps more important in decreasing the cholesterol-phospholipid ratio.

Study of Lipoprotein Cholesterol in 114 Subjects

Harold H. Orvis, Richard C. Fowler, Isa A. Fawal, and John M. Evans, Washington, D. C.

Langen and associates have published a method for the determination of lipoprotein cholesterol which we have confirmed to be relatively simple in terms of time and equipment. Consistently reproducible results are obtained, particularly with respect to the percentage distribution of cholesterol in the α and β fractions. It is the purpose of this report to present certain data from 500 analyses in 114 normal subjects and patients.

Blood from 6 individuals was sampled biweekly for 6 to 8 months, during which time the standard deviation for the per cent of β lipoprotein choles-

terol (PBC) of each ranged from 1.1 to 3.0 per cent with an average of 1.7 per cent. Essentially no change in the PBC was noted in hourly samples from fasting or postprandial subjects.

The upper limit of normal for PBC was fixed at 83 for males and 80 for females. When analyzed by age, the highest fraction of males with elevated PBC was in the 40- to 60-year group, whereas the highest fraction of females with elevated PBC was in the 60- to 80-year group. Obesity did not appear to be a significant factor in any age group. However, the majority of hypertensive patients in the 40- to 60-year group had elevated PBC.

Of 37 patients with angina or myocardial infarction, PBC exceeded the normal in 22, 27 had hypercholesterolemia above 250 mg. per cent and 17 of the 37 had both abnormalities. It is apparent that 32 (86 per cent) of the 37 had a lipid disorder by these criteria. In contrast, about one-third of unselected "normal" subjects have similar lipid findings.

It is concluded that the distribution of cholesterol in the α and β fractions for any given individual is quite constant. Furthermore, the fasting state is unnecessary for sampling. It is suggested that the PBC in combination with total cholesterol will detect a significantly greater number of lipid abnormalities in patients with coronary artery disease than either test alone.

Rapid Measurement of the pCO_2 of the Pulmonary Artery in Man: Clinical Use in the Diagnosis of Congenital Heart Disease in 75 Patients

John J. Osborn,† San Francisco, Calif.

A method will be described for the rapid measurement of the carbon dioxide tension of the pulmonary artery. The method consists of supplying the patient (through an appropriate pneumotachygraph head) with a descending concentration of carbon dioxide in air over a period of 10 seconds. During this time a continuous record is made of respiratory rate, volume, and carbon dioxide concentration. In the presence of relatively normal pulmonary function, a rather exact point is found at which air enters and leaves the lungs without essential change in carbon dioxide concentration. This point of equilibrium is easily found in most patients within 8 seconds and must be in equilibrium with the CO_2 tension of the pulmonary artery.

In clinical use, a record is first made of respiration and carbon dioxide concentration for several breaths. From this record the carbon dioxide concentration of the alveolar air (which is essentially equivalent to pCO_2 of the pulmonary vein) can be approximated, and, at the same time, total excretion of carbon dioxide can be calculated. This record of normal respiration is ended with a measurement of pCO_2 of the pulmonary artery as described. Therefore, by a record made in only 20 to 30 seconds, all of the measurements necessary for the calculation of arteriovenous difference (for CO_2) and pulmonary blood flow are available.

These measurements neither require blood samples nor cooperation by the patient. They have been made on patients of all ages from premature infants to adults. We shall show examples of their use in estimating left-to-right shunting of blood, in estimating peripheral or pulmonary vascular (or valvular) resistance, and cardiac reserve. This method is particularly useful in allowing easy and rapid comparison of rest with exercise in the same patient.

The limitation of the inherent errors in the technic, together with its ease and flexibility, will be discussed.

Serum Glutamic-Oxalacetic Transaminase in Pulmonary Infarction

Bernard H. Ostrow, Howard E. Ticktin, Benjamin S. Buteler, and John M. Evans, Washington, D. C.

In earlier studies it was noted that pulmonary embolization was occasionally followed by increased activity of serum glutamic-oxalacetic transaminase (S-GOT), occasionally in association with jaundice. The present study of acute pulmonary embolization was designed to define the pattern of S-GOT activity and its pertinent etiologic factors.

Twenty-nine patients were studied, and the following observations were made serially, usually over a 7-day period: S-GOT, electrocardiogram, posteroanterior and lateral chest films, liver function battery, and the benzidine test for hemoglobin (hemolysis). Pulmonary embolization was diagnosed by standard clinical criteria; pulmonary infarction was accepted only in the presence of roentgenographic evidence.

S-GOT exceeded 40 U. per ml. in 14 of the 29 patients (48 per cent). The mean peak activity appeared on the fifth day following onset of symptoms and reached 61 U. per ml. The incidence of elevated transaminase was higher in pulmonary infarction (60 per cent) than in embolization (27 per cent), and the mean peak values were higher following pulmonary infarction (62 U. per ml.) than in embolization (43 U. per ml.).

There was liver impairment in all patients in whom transaminase was elevated. However, liver functions were abnormal in several cases of pulmonary embolization or infarction in whom S-GOT was normal. The serum hemoglobin determination revealed no evidence of hemolysis. There was no evidence of associated myocardial infarction.

In view of the relatively small concentration of this enzyme in the lung, it is impossible to explain the increased serum transaminase activity solely on the basis of enzyme liberation from the involved

tissue. Since the incidence and levels of S-GOT were higher in patients with pulmonary infarction, it is suggested that a responsible factor is increased enzyme liberation from the infarcted lung in the presence of altered hepatic function.

It is apparent that the majority of patients with roentgenographic evidence of acute pulmonary infarction show a minimal delayed rise of S-GOT in contrast to the prompt maximal rise following myocardial infarction. The characteristic differences in the transaminase curve may be helpful in differentiating pulmonary from myocardial infarction.

Studies on Dogs with Artificially Created Ductus Arteriosus and Proximally Placed Coarctation of the Aorta

Horacio Padilla, Thomas B. Ferguson, David Goldring, M. Remsen Behrer, Alexis F. Hartmann, Jr., Wilbur A. Thomas, Harvey A. Humphrey, and Charles Crawford, St. Louis, Mo.

We have been impressed by the high mortality rate of infants born with coarctation of the aorta proximal to a patent ductus arteriosus. When, however, these congenital defects occur singularly, the threat to survival is not so serious. It has been noted in some of these infants with the combined defects that there may be reversal of flow through the patent ductus. The explanation for this is not entirely clear. We thought, therefore, it would be of interest to produce these defects artificially in dogs and make physiologic studies of the altered hemodynamics.

The following experiments were carried out: Group I—seven adult dogs were prepared with a fistula between the left pulmonary artery and aorta. Proximal to this defect a slowly developing constriction of the aorta was initiated. Group II—8 adult dogs were prepared with an artificially created ductus arteriosus alone. Group III—in these adult dogs a slowly developing aortic constriction was started distally to the origin of the left subclavian artery.

All dogs had initial base line studies and subsequent observations at periodic intervals until death. These studies included pressure determinations and blood oxygen saturation of both the right side and systemic circulations. Radiographic and electrocardiographic studies were also included and, after death of the animals, appraisal of the pathologic anatomic changes was made.

The results revealed that the dogs in groups II and III lived from 5 to 9 months and, although all developed varying degrees of cardiomegaly, they all did comparatively well when compared with the dogs in group I.

In contrast, the dogs in group I lived only from 13 to 56 days, and all died in congestive failure. Thus, as in infants, the combination of coarctation of the aorta and a distally placed patent ductus arteriosus is incompatible with survival of more than 1 to 2 months. All dogs in this group showed marked dilatation and hypertrophy of both ventricles. The intimal changes in the pulmonary arteries and arterioles, however, were surprisingly minimal. Although all dogs developed marked right ventricular and pulmonary arterial hypertension, none demonstrated a reversal of blood flow through the patent ductus arteriosus.

The significance of these findings is that: (1) The defects may have to be produced in very young animals and persist for a longer time than the experimental period for anatomic changes to appear in the pulmonary arterioles; and (2) these experiments suggest that the surgical obliteration of a patent ductus arteriosus in babies born with coarctation and patent ductus arteriosus may be a life-saving temporizing procedure.

Effects of pH and Oxygen and Carbon Dioxide Concentration Upon Activity of Embryonic Chick Heart

George H. Paff, Robert J. Boucek, and Nancy L. Noble, Miami, Fla.

The ease of observation of the chick embryo heart preparation facilitates the direct study of myocardial activity. Effects of changes in percentages of oxygen and carbon dioxide in the incubation atmosphere on the chick embryo heart were investigated in order to determine the gaseous conditions which would critically stress the heart. A chick heart preparation subjected to this stress could then be used as a bioassay tool to evaluate different metabolic precursors and intermediates upon the activity of the heart.

Each experimental group included approximately 30 hearts. Six hearts isolated from 3-day chick embryos were placed in small drops of blood plasma on the side of a vial with inlet and outlet tubes to permit the introduction of the gases. After the drops of plasma clotted, Tyrode solution was introduced into the vial and, by rotation of the vial, the clots were intermittently bathed with the solution. Microscopic observations of the rate and rhythm of the pulsating heart were made in an atmosphere of air, and these findings were considered control values. A gas mixture was then introduced, and after 13 and 26 minutes of equilibration, additional observations were made. The tube was flushed with air and, after 13 minutes of equilibration, a final reading was made. Changes in the rate and rhythm or the appearance of asystole were noted.

No irreversible deleterious effects upon the activity of the heart were noted when the percentage of oxygen was reduced from 20 to 8 per cent in an atmosphere containing 4 per cent CO_2. Further hypoxia induced a profound rate reduction and the appearance of arrhythmias. These arrhythmias consisted of varying degrees of sinoatrial,

ventricular, and conal block. Absolute anoxia resulted in complete asystole which could be maintained for a period of one-half hour before permanent damage was evident.

In the absence of CO_2, hypoxia resulted in the appearance of profound cardiac stress at an oxygen concentration of 12 per cent. Total anoxia, in the absence of CO_2, resulted in the appearance of irregularities and irreversible asystole. Concentrations of 2 to 25 per cent CO_2, in the absence of oxygen, induced a reversible asystole. Higher concentrations of CO_2 caused irreversible arrhythmias and asystole.

Apparently the severest stress was induced by hypoxia in conjunction with mild alkalosis (approximately pH 7.8 to 8.0). In an acid media of approximately pH 6.8 to 7.0, total anoxia for one-half hour did not affect the recovery of the heart preparation.

Effect of Fibrinolytic Agents on the Vegetations of Experimental Bacterial Endocarditis

Brent M. Parker, Donald C. Andresen, Wilbur A. Thomas, and John R. Smith, St. Louis, Mo.

It has previously been demonstrated that the vegetations of bacterial endocarditis are important barriers to the effectiveness of host resistance factors and antibiotics. This study was undertaken in an effort to determine whether such vegetations could be significantly altered by fibrinolytic agents.

Under sodium pentobarbital anesthesia, mitral and/or aortic valve damage was produced in dogs with a laryngeal biopsy forceps introduced through the right common carotid artery. After an adequate postoperative observation period, a suspension of streptococcus mitis (viridans) was given intravenously. Of 42 dogs subjected to this procedure, 27 developed clinical and pathologic evidence of bacterial endocarditis on the mitral and/or aortic valves. A portion of this group was then given a number of intravenous injections of a saline solution of streptokinase-streptodornase in sufficient concentration to produce partial or total clot lysis of blood drawn 15 minutes after administration of the enzymes. No antibiotics were administered during the course of the study.

Analysis of the results revealed no statistically significant prolongation of life in those animals given streptokinase-streptodornase as compared to a control group that did not receive these agents. Comparison of the size and extent of the vegetations in control dogs contrasted with a similar group given enzymes showed that while 11 of the 14 in the control group had moderate to large vegetations, only 3 of the 9 animals in the latter group had large vegetations. Because of the small numbers involved, these data are not statistically significant at the 5 per cent level. Nevertheless, we feel that these results at least suggest that in some instances, intravenous fibrinolysis favorably alters the vegetations of bacterial endocarditis.

Success of Niacin and Failure of Niacinamide in Reducing Plasma Cholesterol Levels in Patients with Hypercholesterolemia

William B. Parsons, Jr., and John H. Flinn, Madison, Wis.

Large oral doses of niacin (3 to 6 Gm. daily) were administered to 24 patients with hypercholesterolemia. For the first 12 weeks, a daily dose of 3 Gm. was used. If the plasma cholesterol level was higher than 250 mg. per 100 ml. after 12 weeks, the daily dose was increased to 4.5 Gm. and later to 6 Gm. per day in some cases, depending on the response. After 30 weeks, niacinamide was substituted in dosage equal to the most effective dose of niacin. Patients continued with their customary diets.

Eight patients (group I) have been followed for 34 to 42 weeks, and 16 additional patients (group II) for 12 to 32 weeks. The mean plasma cholesterol level, for all 24 patients, fell from 325 mg. per 100 ml. before treatment to 269 mg. per cent after 2 weeks, and to 263 mg. per cent at the end of 12 weeks of niacin therapy.

Significant reduction in plasma cholesterol levels has thus far been observed in 16 of 24 patients (66.7 per cent) followed for 12 to 42 weeks, including 7 of 8 patients (87.5 per cent) followed for at least 30 weeks (group I). Seven of the 8 patients who have not shown significant reduction have not yet received doses of 6 Gm. daily, inasmuch as they have been treated for shorter periods (group II).

Of the 8 patients of group I, 6 had normal plasma cholesterol levels (less than 250 mg. per cent) after 30 weeks, and the level in 1 of the remaining 2 patients had been significantly reduced (480 to 262 mg. per cent) but not to normal. Group I showed a mean plasma cholesterol level of 334 mg. per cent before treatment, 270 mg. per cent after 2 weeks, 266 mg. per cent after 12 weeks, and 252 mg. per cent after 30 weeks of niacin therapy.

Doses of 4.5 or 6 Gm. of niacin per day were required in more than 50 per cent of patients. Of 5 patients who received 6 Gm. daily, plasma cholesterol levels reached normal in all but 1 and were consistently normal in 3. Based on these results, similar improvement is anticipated in 7 other patients who have failed to respond to 4.5 Gm. daily who will now receive larger doses.

Substitution of niacinamide resulted in prompt return of plasma cholesterol to pretreatment levels in every instance. The absence of significant side effects or toxic effects previously reported by Parsons et al., was confirmed.

The results suggest that the use of large doses of niacin may prove to be the most practical method introduced to date for reduction of elevated plasma

cholesterol levels to normal without dietary restriction.

Circulatory Changes Associated with Pulmonary Valve Obstruction During Cardiac Catheterization

Milton H. Paul and Abraham M. Rudolph, Boston, Mass.*

A serious and not infrequent complication of cardiac catheterization has been encountered in 8 patients with severe pulmonary stenosis. Our experiences indicate that this complication can occur in both a manifest, symptomatic form, and in an occult, asymptomatic form.

During cardiac catheterization in 31 infants and children with pulmonary valve stenosis and intact ventricular septum, hemodynamic changes indicating obstruction of the pulmonary valve by the exploring catheter were observed in 8 (or 25 per cent) of the patients studied. In 6 patients, acute clinical evidence of the obstruction was observed: apprehension, increasing cyanosis, myoclonic contractions, and, in 1 instance, hemiparesis of several days duration.

Nine of the 31 patients studied showed arterial oxygen unsaturation at rest, and the 8 patients with signs of pulmonary valve obstruction were in this group with arterial unsaturation. The resting pulmonary blood flows in the obstructed group (2.1 L. per minute per $M.^2$) were significantly lower than in the nonobstructed group (4.8 L. per minute per $M.^2$). The pulmonary valve size, as calculated by the Gorlin formula, was less than 0.15 $cm.^2$ in all patients with evidence of valve obstruction during the catherization.

Once the cardiac catheter was passed through a severely stenosed pulmonary artery valve, it further significantly reduced the orifice area. The pulmonary blood flow, already subnormal, was observed to fall even further to very low levels. There was a marked reduction (up to 25 per cent oxygen saturation) in mixed venous and arterial oxygen saturation. The decreased arterial oxygen saturation was associated with an increase, or relative increase, of the right-to-left shunt through an atrial communication. The right ventricle, already functioning at its maximum level, was unable to meet the demands placed on it by the presence of the catheter in the pulmonary valve.

Uncommon Types of Cardiovascular Disease Associated with Free Aortic Regurgitation into the Heart

Oglesby Paul, John S. Graettinger, and Arnold Brown, Chicago, Ill.

The clinical picture of a free aortic regurgitation (including particularly a wide pulse pressure with peripheral evidences, and a decrescendo diastolic murmur along the left sternal border) is almost always associated with organic aortic cusp disease due to rheumatic fever, or to separation of the cusps associated with syphilitic aortitis.

Other uncommon types of free aortic regurgitation into the heart (thus excluding aortic-pulmonary artery fistulas) exist, some of which are now amenable to surgery, and must therefore be properly identified.

Four uncommon groups of conditions associated with a free aortic regurgitation have been studied during life and at the autopsy table: 1. Congenital heart disease associated with a high ventricular septal defect, involving the aortic valve ring. A 24-year-old male is studied clinically (including by cardiac catheterization and angiocardiography), and later at autopsy. 2. Congenital heart disease associated with coaretation of the aorta and a bicuspid aortic valve. A 30-year-old male is studied clinically and later at autopsy. 3. Rupture of a sinus of Valsalva into the right atrium or ventricle. Cases include that of a 56-year-old male with rupture into the right ventricle, studied clinically and at autopsy. 4. Dissecting aneurysm of the aorta with separation of the aortic cusps and a free regurgitation into the left ventricle. A 39-year-old male, masquerading as rheumatic heart disease with mitral and aortic valve involvement, is studied clinically and at autopsy.

Mechanisms of Fixed Splitting of the Second Heart Sound

Joseph K. Perloff and W. Proctor Harvey, Washington, D. C.

Twenty normal subjects with physiologic splitting and 33 patients with wide splitting of the second sound (S_2) were studied with fast speed high frequency phonocardiograms. The dicrotic notch of synchronous carotid or pulmonary arterial pulses identified aortic (A_2) and pulmonic (P_2) valve closures. All recorded events were appreciated by auscultation. Cardiac catheterization confirmed the diagnoses in the congenital and rheumatic groups.

In 20 normal subjects, inspiratory augmentation of right heart filling prolonged the right ventricular stroke time and delayed P_2, thus altering the second sound from expiratory synchrony to inspiratory splitting.

In 8, atrial septal defects S_2 normalized postoperatively, reflecting the right ventricular capacity to undergo its normal inspiratory increase and expiratory decrease in stroke volume when the defect was closed. Before closure right ventricular stroke time neither shortened with expiration nor lengthened with inspiration because of constant right ventricular hypervolemia. Hence, preoperatively the A_2-P_2 split remained wide and fixed.

Six patients with pure mitral incompetence had wide splitting of S_2 because A_2 occurred early. In

3 with compensated right ventricles, splitting widened with inspiration and narrowed with expiration. In 3 with right ventricular failure splitting remained fixed. Ten with complete RBBB had wide splitting because P_2 was delayed. In 7 with compensated right ventricles splitting widened with inspiration and narrowed with expiration. In 3 with right ventricular failure splitting remained fixed. Ten with complete LBBB had split second sounds because of reversed sequence of aortic-pulmonic valve closure. In 4 with compensated right ventricles, S_2 split on expiration and became single on inspiration. In 3 with right ventricular failure splitting remained fixed.

Evidence suggests in the 9 patients with right ventricular decompensation, the failing chamber could *not* convert inspiratory augmentation of flow into increased stroke volume, hence P_2 was not delayed during inspiration and the A_2-P_2 interval (split S_2) remained fixed throughout respiration.

Mechanism of Murmur of Tricuspid Stenosis

Joseph K. Perloff and W. Proctor Harvey, Washington, D. C.

The nature of selective inspiratory augmentation of the murmur of tricuspid stenosis was studied in 4 patients. Almost invariable coexistence of mitral stenosis warrants emphasis on this clinical feature which could distinguish these lesions. Diagnoses were established by cardiac catheterization and confirmed at surgery. All 4 patients had associated mitral stenosis. Three had trivalvular stenosis. Phonocardiograms were fast speed, high frequency recordings.

Three patients had sinus rhythms and revealed marked selective inspiratory increase in presystolic murmurs at the left sternal edge. The fourth patient had atrial fibrillation and the mid-diastolic murmur waxed markedly during inspiration and waned with expiration.

The following mechanisms were hypothesized: (1) That the right atrium could not freely transfer its contents across the stenotic tricuspid valve as evidenced by the invariably gentle Y descent of the right atrial pulse; (2) that rapid inspiratory augmentation of right atrial filling might magnify this deficit; (3) that these pressure-flow alterations should not occur in mitral stenosis because pulmonary veins, left atrium, and left ventricle share equally the respiratory changes in intrathoracic pressure. The first 2 postulations should produce (a) increased tricuspid flow during the Y descent, hence increased intensity of the mid-diastolic murmur, and (b) increased tricuspid gradient at the end of the Y descent, hence increased presystolic murmur as the atrium contracted against this augmented gradient.

Simultaneous right atrial-right ventricular pulses were recorded with double lumen catheters. Inspiratory increase and expiratory decrease of tricuspid gradient was demonstrated. Simultaneous left atrial-left ventricular pulses were recorded bronchoscopically in one mitral stenotic. The mitral gradient did not increase with inspiration.

It appears that in tricuspid stenosis, inspiratory augmentation of right atrial filling cannot rapidly be transferred across the stenotic valve, thus producing an inspiratory rise in right atrial pressure, an inspiratory increase in gradient and, consequently, an inspiratory increase in tricuspid stenotic murmur.

Psychosomatic Basis of Essential Hypertension

Robert S. Picard, Shreveport, La.

This paper presents the author's findings of certain recurrent personality patterns in the psychosomatic make-up of approximately 70 patients with essential hypertension. It is offered, particularly, to present workable systematized psychosomatic procedures for handling these people rather than the more difficult "individualization," insisted on as being necessary in the past.

In these cases it was noted that in any patient with hypertension who admitted: (1) an inability to express hostility, (2) an excessive empathy, and (3) an abnormal concern about dying, the diagnosis of essential hypertension could be made as a positive rather than an exclusion diagnosis. These findings are related to the development by these people in early childhood of abnormally sensitive responses to the feelings of others. The basis of this is felt to be the immature approach by their parents towards responsibilities, illnesses, or hardships, and their consequent craving of sympathy from the prehypertensive child. The contributing and precipitating stresses: the marriage pattern and work pattern, and the hypertensive's repression of hostility are explored.

Emphasis is placed on relying on history, subjective feelings of the patient, progressive physical findings, serial laboratory and x-ray work, rather than the rise and fall of the sphygmomanometric readings as an index of progress or regression of hypertension.

Therapeutically, the needs of not communicating the doctor's anxiety about elevated blood pressure readings, of encouraging the patient to work, to find a hobby, of assisting him to express hostility not only in the doctor's office but in his daily activity, of helping him live with his excessive empathy and of easing his distrust of death, are examined as means of lengthening life span and reducing morbidity in essential hypertension.

Effects of Isuprel in Advanced A-V Block

Alfred Pick and Alvin Lichtman, Chicago, Ill.

The effects of the cardiac mechanism of single and repeated intramuscular injections of 0.1 to 0.2

mg. isopropyl-norepinephrine (Isuprel) were studied in serial electrocardiograms of 5 patients with A-V dissociation due to advanced A-V block. In 2 of the cases, 1 with atrial fibrillation, the A-V block was considered to be complete, in view of a slow ventricular rate. Isuprel accelerated the atrial action (by 80 per cent) in the one with sinus rhythm, and the A-V nodal rate in both (by 30 and 50 per cent respectively). Suppression was thereby effectively accomplished in 1 case of an idioventricular rhythm, which was competing for ventricular activation with an unstable A-V nodal pacemaker. In the other 3 cases, a low ratio of atrial and ventricular rates suggested that the block might be incomplete. This was confirmed in 1 case by occasional retrograde activation of the atria by the nodal impulse with re-entry into the ventricles. This later mechanism, in turn, caused a repetitive ventricular response with resultant prolonged attacks of ventricular tachycardia and transient ventricular fibrillation, thus giving rise to Stokes-Adams attacks. Following Isuprel, the sinus rate was accelerated in 2 of the cases (25 and 80 per cent respectively) and A-V nodal activity was suppressed in all 3, due to transient restoration of A-V conductivity at A-V ratios varying between 3:1 and 5:4. Consequently, the re-entry phenomena with syncopal attacks were also suppressed in the case mentioned. Except for occasional ventricular premature beats in 1 instance, no direct effects of the drug were seen on lower ventricular pacemakers, even after repeated injections. It appears, therefore, that the known beneficial effects of Isuprel in the management of the various complications of A-V block are mediated by 2 different mechanisms: (a) in complete A-V block by acceleration of supraventricular pacemakers; (b) in incomplete A-V block (with A-V dissociation) by improvement of A-V conductivity leading to secondary suppression of activity of all subsidiary pacemakers.

Further Studies on the Sequelae of Miliary Pulmonary Embolism

Ruth Pick, Donald Singer, C. Hesser, and Louis N. Katz, Chicago, Ill.

Previous studies from this department showed that unilobar miliary pulmonary embolism resulted in the production of an incomplete local infarction and diffuse bilateral pulmonary edema in anesthetized and unanesthetized dogs. The predominately unilateral distribution of starch was previously demonstrated histologically. The validity of this method for the determination of starch distribution was checked by another technic. In 27 dogs a section of each lung lobe was first removed for histologic evaluation. Each lobe was then separately homogenized in a Waring-type blender containing Ringer's solution. An aliquot was removed, transferred to a slide and stained with Lugol's iodine for the demonstration of starch granules. A granule count was then accomplished by microscopic examination. This yielded an excellent correlation with the histologic technic. A small number (0–10) of granules was frequently seen in the noninjected lobes. To analyze the importance of this for edema formation, the usual amount of starch (1 Gm.) was injected into the right ventricle of 5 dogs, resulting in a fairly even distribution of granules throughout both lungs. Under these experimental conditions, pulmonary edema did not occur. These findings indicate that diffuse pulmonary edema can be produced by unilateral embolization with infarction and that its mechanism is unrelated to the minimal spill-over of embolizing material into contralateral lobes. A neurogenic or neurohumoral mechanism has been postulated as the mechanism of the edema on the contralateral, noninjected side.

Evaluation of Quantitative Methods for Obtaining Mean Spatial QRS Vectors

Hubert V. Pipberger, Washington, D. C.

The mean QRS vector has often been loosely defined and needs critical evaluation. In the present study the true mean QRS vector is defined as the integration of the magnitude *and* time of all spatial instantaneous vectors during QRS. These were obtained by vectorial addition of instantaneous vectors at intervals of 0.0025 sec. Vectorcardiograms and scalar leads were recorded in 17 normal subjects and 17 cardiac patients using Schmitt's SVEC III. Vectors close to point E were checked against scalar leads and reconstructed when necessary on enlarged records. The inherent error of this method was 0.0041 ± 0.0027 second or 8.8 ± 5.8°. This error was minimized by averaging the results obtained in 3 planes.

This time-consuming procedure was next compared with simpler methods, suitable for routine use. *Maximal vectors* or vectors of largest magnitude were determined in each plane. The error of this method was large, as maximal vectors frequently differed in different planes. The error in the cardiac patients averaged 0.012 ± 0.0101 second or 15.4 ± 12.9°. For the total of both groups the average of the 3 planar maximal vectors differed from the true mean spatial vectors by 0.0041 ± 0.0031 second or 8.8 ± 6.6°. *Half-time vectors* were obtained by dividing QRS in time. The correlation with the true mean vectors was poor. *Half-area vectors* were obtained by dividing QRS-loops planimetrically in 2 equal parts in each plane. Correlation with the true mean vectors was good and was enhanced further by averaging the 3 planar vectors. The

difference between the average half-area and true mean spatial vectors (0.0021 ± 0.0023 second or 4.5 ± 4.9°) seemed negligible in view of the inherent errors of all graphic methods.

These results indicate that the most reliable yet simple method for obtaining representative QRS vectors was the determination of the planar half-area vectors. Correlation with the true mean spatial vectors was excellent when the half-area vectors in the 3 planes were averaged.

Simplified Resolver for Obtaining Corrected Electrocardiograms

Hubert V. Pipberger, Washington, D.C., and Robert C. Wood Jr., Silver Spring, Md.

There is some evidence to suggest that conventional precordial leads may supply, by recording preferentially from local underlying portions of the heart, additional information not provided by the corrected systems. This problem can be studied by using a resolver which will provide leads derived from orthogonal systems. These leads obtained at regular angular intervals in 3 planes can then be correlated with conventional electrocardiograms. To facilitate the collection of such data in large series a simple and inexpensive type of resolver was designed.

Resolvers used in the past required sine-cosine potentiometers with additional vacuum tube stages (Schmitt) or continuous preamplifier adjustments (Brody). In the type described here, advantage was taken of the high strength of corrected leads. Orthogonal components X, Y and Z are fed into preamplifiers characterized by 20 megohms differential input, 1,000 ohms single-ended output and gain of 100 from 0.1 to 10,000 c.p.s. Preamplifier outputs are fed to the resolvers XY, XZ and YZ. These are arranged to yield outputs:

$$XY = X \cos \Theta + Y \sin \Theta$$

$$XZ = X \cos \Theta + Z \sin \Theta$$

$$YZ = Y \cos \Theta + Z \sin \Theta$$

Polarity switches provide coverage of all quadrants of 3 planes. The resolvers allow recording of leads switched in 15° steps. Two voltage dividers are used for each resolver, one for $\sin \Theta$ and one for $\cos \Theta$, their outputs being added by simple resistance adding networks. These are designed to be driven by 1,000 ohms preamplifiers and are compensated for the loading effect of the adding resistors. The 3 orthogonal leads (attenuated the same as the resolvers) and the output of the resolvers are fed to 4 output switches allowing selection of any of those leads for a conventional 4-channel ECG recorder.

Phonocardiogram in Mitral Valvular Disease: Correlation with Left Heart Catheterization and Operative Findings

Munro H. Proctor, Boston, Mass., Rhett P. Walker, Mobile Ala., Ernest W. Hancock, and Walter H Abelmann,† Boston, Mass.*

It has been reported that the interval between the QRS of the electrocardiogram and the first heart sound (Q-1) varies directly and the interval between the second heart sound and the opening snap inversely with the degree of mitral stenosis. A phonocardiographic study of 49 patients with mitral valvular disease proven by left heart catheterization (32) or operation (34) revealed the value and limitations of this approach.

Q-1 averaged 0.07 seconds ± 0.003 (S.D.) in patients with mitral stenosis, significantly longer than in 23 control subjects (0.05 seconds ± 0.01). There was little correlation between Q-1 and severity of mitral stenosis, end-diastolic pressure gradient and left atrial mean pressure. An inverse relationship between Q-1 and the preceding R-R interval existed in mitral stenosis as well as mitral insufficiency unless the insufficiency was "pure" and without pressure gradient. In the latter case, Q-1 was in the control range.

An opening snap was demonstrable in 31 patients. Eight others had minimal or no stenosis and 7 had heavily calcified valves. The 2-OS averaged 0.08 seconds ± 0.02. A 2-OS interval of 0.08 seconds or less was always associated with at least moderate stenosis (16 cases), while a longer interval was seen in 4 cases of severe and in 6 cases of moderate stenosis.

The 2-OS showed significant correlation with left atrial mean pressure ($r = 0.7$), and less correlation with mean diastolic pressure gradient ($r = 0.4$). The data suggest that 2-OS is determined by left atrial pressure rather than by degree of stenosis or regurgitation.

All 24 patients with Q-1 greater than 0.06 seconds *and* 2-OS less than 0.09 had moderate or severe mitral stenosis. After successful valvuloplasty Q-1 always decreased and 2-OS usually increased.

Splanchnic Blood Volume in Congestive Heart Failure

Elliot Rapaport, San Francisco, Calif., Myron H. Weisbart, and Milton LeVine, Albany, N. Y.

Splanchnic plasma volume (T-1824 space) was measured in 12 patients with moderate to severe congestive heart failure and splanchnic blood volume approximated by use of the large vessel hematocrit. The results were compared with similar studies in 10 normal patients.

Estimated hepatic blood flow was frequently reduced in patients with congestive heart failure;

however, this reduction generally was in proportion or, if anything, less than the reduction in cardiac output. Splanchnic oxygen uptake remained essentially unchanged. As a result, arterial-hepatic venous oxygen difference was significantly greater among the patients with congestive heart failure. Total blood volume averaged 62.1 ml. per Kg. (S.D. 7.0) among control patients and was significantly increased to a mean of 79.8 ml. per Kg. (S.D. 12.5) in the patients with congestive heart failure. Splanchnic blood volume averaged 12.7 ml. per Kg. (S.D. 2.2) among the control patients and was markedly increased in the group with congestive heart failure to a mean of 20.8 ml. per Kg. (S.D. 5.6).

The results indicate that the splanchnic blood volume is increased in many patients with congestive heart failure and serves as a major reservoir for the observed increased total blood volume. It would also appear that splanchnic blood volume is not solely regulated as a function of the splanchnic arteriolar resistance but that splanchnic pooling may occur from the effects of a distending venous pressure on a relatively elastic capillary-venous bed.

Experimental Observations Suggesting a Possible Rationale for Use of Molar Sodium Lactate in Treatment of Cardiac Arrhythmias

Raymond C. Read, Hiroshi Kuida, John A. Johnson, and C. Walton Lillehei, Minneapolis, Minn.*

The use of molar sodium lactate has been advocated in the clinical treatment of cardiac arrhythmias arising spontaneously or as a result of intracardiac surgery.

Observations have been made during the course of hemodynamic studies in the totally perfused dog which provide experimental evidence of the efficacy of this drug. Fifty to 100 ml. of isotonic and molar solutions of either sodium chloride, hydroxide, bicarbonate, lactate or 50 per cent glucose were infused into 21 dogs during cardiopulmonary bypass at constant rate (50 to 120 ml. per Kg. per minute), with induced ventricular fibrillation. Spontaneous defibrillation occurred in 5 out of 7 instances when molar sodium lactate was used and was not seen with any of the other agents. Isotonic solutions had no vasomotor activity, whereas infusion of the hypertonic solutions at more than 3 ml. per minute in each instance resulted in an absolute increase in coronary blood flow despite a uniform fall in arterial pressure. These changes were unrelated to alterations in pH or pCO_2.

These results indicate that molar sodium lactate has a dual effect on the heart, a specific defibrillatory action accompanied by coronary and systemic vasodilatation, the latter being associated with the hyperosmolarity of the infused solution.

Postoperative Sequelae with the Bubble Dispersion Type Oxygenator: Antifoam Toxicity

William A. Reed and C. Frederick Kittle, Kansas City, Kan.

Utilizing a bubble dispersion disposable oxygenator, 17 consecutive dogs were perfused for 2 hours with total cardiopulmonary bypass. Sixteen animals survived, 1 dying 12 hours postperfusion. Of the survivors, 8 showed temporary signs of neurologic damage for periods up to 9 days. These symptoms consisted of ataxia, hemiparesis, general apathy, and skew deviation of the eyes. The etiology of these changes includes the possibility of embolization due to air, fibrin, or antifoam.

To investigate the toxicity of the antifoam compound used in this type of oxygenator, 31 dogs were given varying amounts of the antifoam A compound intravenously. An intravenous dose of 0.9 ml. or more per Kg. produced death within several minutes in 50 per cent or more of the animals tested (LD_{50}). Death was characterized by acute dyspnea, tachycardia, and hypotension. Autopsies disclosed a dilated right ventricle. When given intra-arterially into the common carotid artery in 15 dogs (as blood is given from the oxygenator in perfusion experiments), a dose of 0.03 ml. or more per Kg. produced either instant death or severe neurologic changes with subsequent death in 50 per cent or more of the animals tested (LD_{50}). Smaller doses resulted in temporary neurologic damage.

Gross and microscopic examinations of these brains disclosed areas of encephalomalacia compatible with embolization. Representative electroencephalograms taken during perfusion and postperfusion frequently showed slowing and decrease in the amplitude of the waves, but these changes did not correlate consistently with neurologic symptoms.

Use of a New Sagittal Lead for Estimation of Ventricular Hypertrophy

Ernest W. Reynolds, Jr., and Franklin D. Johnston, Ann Arbor, Mich.

Precordial leads are more helpful than the limb leads for the electrocardiographic diagnosis of ventricular hypertrophy, but no entirely acceptable criteria, particularly for the estimation of left ventricular hypertrophy, are available. Since it is known that the mean vector of QRS points more posteriorly with left and more anteriorly with right ventricular hypertrophy, it seemed to us that the form of the QRS complex obtained in a good sagittal lead might provide a simple and possibly quite reliable method for the recognition of ventricular hypertrophy.

The authors believe that a multiple electrode grid arrangement over the entire precordial area

and a similar system over the left posterior chest behind the heart give a lead system capable of accurate measurement of the sagittal component of the cardiac electromotive forces. This electrode system provides an excellent lead for the sagittal component of vectorcardiograms taken in the transverse or sagittal planes. For the scalar electrocardiograms employed in this study, the polarity was arranged so that positivity of the anterior electrodes resulted in an upward deflection in the tracing.

In most normal subjects the QRS complexes obtained with this lead are of the transitional type and the R/S ratio is close to one. In patients with left ventricular hypertrophy, the R waves are usually considerably smaller than the S waves, and, with right ventricular hypertrophy, the reverse is true. This means that the R/S ratio is small, usually considerably less than 1 in left and greater than 1 in right ventricular hypertrophy.

At the moment we believe that the R/S ratio in the sagittal lead mentioned may be helpful in estimation of ventricular hypertrophy.

Effect of Nicotine on the Normal and Atherosclerotic Intact and Isolated-Perfused Rabbit Heart

Seymour H. Rinzler, Janet Travell, and Dorothy Karp, New York, N. Y.

Studies were carried out on normal rabbits and cholesterol-fed rabbits with a positive ergonovine test. Nicotine bitartrate 0.05 mg. per Kg. injected intravenously caused depression of the S-T segment in only 2 of 16 rabbits with positive ergonovine tests, and in none of 12 normals The heart rate in both the normal and atherosclerotic rabbits was slowed by nicotine, therefore S-T segment changes could not be attributed to a tachycardia.

The hearts were then perfused in a modified Langendorff apparatus. Initially, before any drug was given, the status of 29 atherosclerotic hearts when compared with 32 normal hearts was found to be significantly different statistically with respect to coronary flow, heart rate, and amplitude of contraction. The initial coronary flow was greater, the rate was slower, and the amplitude of contraction was smaller in the atherosclerotic heart. Nicotine in graded doses of 0.01 to 0.1 mg. was perfused into 6 normal and 7 atherosclerotic hearts. Nicotine caused an initial decrease in flow in every heart. Vasoconstriction was greater for the normal than for the atherosclerotic hearts. A more striking difference related to secondary vasodilatation Following the initial vasoconstriction, a rise in flow occurred in every normal heart, especially after the larger doses of nicotine, but was never observed in the atherosclerotic heart. The decrease in flow lasted longer in the atherosclerotic hearts. Changes in the coronary flow were independent of the brief and slight acceleration of the heart rate. The amplitude of contraction in both groups decreased slightly with the smallest dose of nicotine (0.01 mg.) and increased with larger doses. In summary, the atherosclerotic rabbit heart shows a difference in the coronary flow pattern from the normal heart in its response to nicotine.

Improved Relief of Angina Pectoris by "Sustained-Release, Long-Acting" Forms of Pentaerythritol Tetranitrate (PETN)

Joseph T Roberts, Buffalo, N. Y.

PETN, a long-acting coronary vasodilator of value next to the short-acting, irreplaceable nitroglycerin, has been made available in new form with variably coated granules designed to release the agent in the intestine for absorption at intervals of about 3 hours. This sustained-release PETN, in doses of 30 mg. on arising and at bed time, gave obviously better control of the number and severity of anginal pectoris episodes, the need for nitroglycerin, and improvement in work tolerance than did a placebo of identical appearance in a double-blind controlled study on 42 well-known patients followed for 6 months with 127 cycles of comparison at intervals of 2 weeks or more. As compared with their condition on previous standard management, 8 became "much better," 22 "very much better," 10 "definitely better," and 2 "no better or only a little better" while changing from placebo to PETN, with similar degrees of worse control when on placebo. No significant reactions occurred. This form of PETN is a useful new agent.

Group Therapy or Class Guidance for Heart Disease Patients

Joseph T. Roberts and Daniel S. P. Schubert, Buffalo, N. Y.

Group therapy or class guidance of large numbers of heart disease patients has been used intensively for about 4 years, with participation of hospitalized and home-living patients with various types of hearts disease, their relatives, dietitians, nurses, and others. Frank discussion is given of mechanisms of heart disease in nontechnical language and of any questions raised by the group. Emphasis is usually given to salt or caloric dietary problems, use of Dicumerol on a long-term basis, nitrates, other agents, the place of surgery and psychiatry, and the need to control exercise, stress, sexual life, employment, and desire of cardiac patients to lapse treatments. Skill in conducting such a group therapy session comes only with confidence from practice and continuing evaluation of goals and methods. Advantages include: (1) Repetition of essential principles is easier for the staff and gives better application by patients; (2) increased emotional support and understanding of a patient's problems

because he can express himself emotionally here as possibly nowhere else; (3) other patients are guided by group analysis of problems and needs presented by others. Experiences of others help many patients to avoid future complications. Acceptance of the diagnosis and the need for care is made easier by seeing the activities of progressively improving patients.

Questionnaires confirmed our impressions of this valuable method. Eighty-seven per cent of patients reported "very helpful" guidance generally; 82 per cent profited by dietitians' explanation of foods to the group. Ninety-five per cent "liked to be a member of the group." Ninety-five per cent gained more confidence in their medical program and understood their own problems better; 83 per cent "worry less;" 70 per cent "smoke less." On many major items of analysis, statistically, a "level of confidence" in the results indicated that the benefit from group therapy is greater than that which might be attributed to "placebo effect" of 33 per cent established by Beecher et al. Some patients who resisted group therapy at first became most active enthusiasts for its use after a few sessions. Rarely did patients who seemed to understand critical needs in the class discard all restrictions soon after to their detriment. Group therapy, according to the patients, improved sleep, work tolerance, exercise tolerance and easier breathing, but did not significantly reduce drug intake or heart pain except by indirectly improving therapy.

Mechanisms of Auscultatory Gap or Doubling of Arterial Sounds in Aortic Stenosis

Simon Rodbard and Jan Ciesielski, Buffalo, N. Y.

The arterial sounds heard during blood pressure measurement reveal an auscultatory gap in some patients with aortic stenosis; in others, doubling of the arterial sounds occurs. We have examined 20 patients so diagnosed and have demonstrated that these acoustic phenomena provide information concerning the contour of the arterial pulse wave. Sounds were recorded on a Sanborn Twinbeam, using the simultaneous electrocardiogram as a reference tracing. The time of onset of an arterial sound in a given cardiac cycle is affected by the cuff pressure. In normals, the sound at systolic levels begins about 0.30 second after the Q wave; this time becomes progressively shortened as cuff pressure falls, until at diastolic values it is about 0.20 second. A plot of the times of onset of the sounds against the cuff pressures presents a calibrated contour of the upstroke of the arterial wave. In aortic stenosis, the presence of an auscultatory gap was shown to be associated with a plateau on the upstroke; the pressure peak may not be reached until 0.40 second following Q. The gap also was associated with a reduced extremity blood flow; the gap was widened by a tourniquet on the forearm or eliminated by the increased blood flow of reactive hyperemia. In some patients with severe aortic stenosis no gap is present. Instead, doubling of the arterial sounds occurs. Pulse contours obtained by arterial puncture revealed that this doubling was due to a deep incisura on the arterial upstroke, the second arterial sound representing the time of the sharp rise following a transitory fall in pressure. The indirect determination of the calibrated pulse wave contour thus provides significant diagnostic and clinical information in patients with aortic stenosis and obviates the need for arterial puncture.

Pulmonary Valve in Direct Phonocardiography

William M. Rogers, Erwin Simandl, Shivaji B. Bhonslay, and Ralph A. Deterling, Jr., New York, N. Y.

Difficulties in separating the sound produced by the different structures of the heart, as they are picked up from any area of the chest wall as compositions, have created interest in direct heart recordings.

Since the second heart sound, heard at the pulmonary area plays an important role in diagnosis of heart diseases, it was our purpose to demonstrate clearly the sound produced by the pulmonary valve.

Direct heart recordings have been taken from 20 dogs. Findings at different areas of the heart and great valves are described. Slight or wide splitting of the second sound was recorded from the pulmonary valve in all animals and frequently from the right ventricular outflow tract. By means of simultaneous tracings from different areas, experimental production of pulmonary stenosis, inflow occlusion and removal of the pulmonary valve, the second component of the split sound could be demonstrated to originate from the pulmonary valve. The sound varied considerably in amplitude. The first component of the split sound of more constant amplitude was found to be aortic in origin. It predominated also at the pulmonary valve in most instances. It appears that a sound picked up from the second or third left interspace commonly referred to as pulmonary area cannot reliably be interpreted as pulmonary in origin if splitting cannot be demonstrated.

Of interest was a midsystolic murmur of diamond shape that was invariably recorded from the pulmonary valve. The murmur presumably is identical with the functional murmur found in children and young adults. It disappeared after removal of the pulmonary valve, indicating that this murmur does not only depend on the relation of flow rates and pulmonary orifice but also on the presence of the pulmonary valve.

The method of direct heart recording is being applied to patients subjected to open heart surgery.

Pulmonary Vascular Responses to Serotonin and the Effects of Certain Serotonin Antagonists

John C. Rose,† Washington, D. C.

In intact animals, 5-hydroxytryptamine (serotonin) elevates pulmonary vascular resistance. Since pulmonary hemodynamics are influenced by many extrapulmonary and ventilatory factors, the following experiments were performed to detect direct vascular effects.

Dogs were anesthetized with sodium pentobarbital or urethane and a diaphragm pump of controlled output was substituted for the left ventricle. Blood was drained from the left atrium to a reservoir from which it was pumped to a T-tube in the thoracic aorta. Left ventricular bypass was complete. The right ventricle continued functioning normally.

As serotonin (2 to 80 mEq. per Kg.) was injected into the pulmonary artery, the tube draining the left atrium was temporarily diverted to a second reservoir. During this period, circulation was maintained by blood pumped from the previously filled main pump reservoir. The drug traversed only the lungs. When the main reservoir was nearly depleted, the atrial tube was returned to its original position, and blood in the temporary container was returned to the circulation.

Confined to the pulmonary vasculature, serotonin caused immediate pulmonary hypertension and decreased blood flow (pulmonary resistance up to 200 per cent of control). Similar pressure and flow changes followed the same dose when given at 5-minute intervals. Only serotonin produced pulmonary vascular effects in doses insufficient to affect systemic arterial pressure.

Systemic vascular reflexes were not initiated by serotonin in the lungs. (These reflexes are easily demonstrated in this preparation using veratrum.) Airway pressure usually did not rise until serotonin entered the systemic circulation (unlike acetylcholine that constricts bronchi as it traverses the lungs).

Promethazine, LSD-25 and its 2-brom derivative (BOL) blocked completely pulmonary vasoconstriction due to serotonin. These were administered previously intravenously in doses from 0.5 to 1.0 mg. per Kg. The serotonin antimetabolite, BAS, followed these in potency. Other "antihistaminics" lacked antiserotonin effect in the lungs.

Change in the Serum Cholesterol and Blood Clotting Time in Men Subjected to Cyclic Variation of Emotional Stress

Ray H. Rosenman and Meyer Friedman, San Francisco, Calif.

The possible effects of emotional stress upon the serum cholesterol and blood clotting time of 42 volunteer male accountants (ages 28–56) were studied during the first 6 months of 1957. These men were selected because of the unique phasic variations of their work load and its associated "deadline" work periods (January 1–15; March 1–15; April 1–30). Serum cholesterol and blood clotting time were determined bimonthly. In addition, careful records were made of (1) other possible emotional stresses, (2) weight, (3) exercise, and (4) dietary intake. The following results were obtained:

Among the 42 accountants a significant increase of serum cholesterol up to 125 mg. per 100 ml. occurred at the times of considerable stress. In 83 per cent of the entire group, the maximum cholesterol (260 mg. per 100 ml.) ($S.E._M$ ±8.8) observed in each individual during the study period occurred at the times of their maximal stress. Conversely, in 76 per cent of the entire group, the individual's minimum observed cholesterol (197 mg. per 100 ml.) ($S.E._M$ ±5.7) occurred at the times of their least stress.

Even more striking was the highly significant acceleration of blood clotting time which shortened from an average of 9.4 minutes during the interval of minimum stress to 5 minutes at the time of maximal work stress.

The results could not be ascribed to changes of exercise pattern, diet, or weight. It is concluded that temporal periods of unusual emotional stress and tension are frequently accompanied by highly significant increases of serum cholesterol and acceleration of blood clotting time.

Hemodynamic Observations in 23 Patients with Pure Mitral Insufficiency

John Ross, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

Left and right heart catheterizations were carried out in 23 patients in whom mitral insufficiency was the sole valvular lesion. This diagnosis was established at operation, by transbronchial left heart catheterization, or at autopsy.

Left atrial z point pressures exceeded 15 mm. Hg in 17 of 23 patients and left ventricular end-diastolic pressures were similarly elevated in 7 of 12 patients. The left atrial pressure pulse contours were diagnostic in 20 patients on the basis of criteria relating to the rate of the y descent and mean left atrial pressure. In the remaining 3 patients a typical left atrial pressure curve was obtained during infusion of norepinephrine. Left atrial pressure contour analysis was found to be of considerably greater diagnostic value than the wedge pressure tracing.

Pulmonary artery or right ventricular systolic pressure exceeded 55 mm. Hg in 10 patients. Pulmonary arteriolar resistance was strikingly elevated in the 5 patients in whom this determination was made. Histologic examination of the lungs in 5 of the patients with pulmonary hypertension re-

vealed extensive proliferative changes in the pulmonary arterioles.

Late Hemodynamic Complications of Anastomotic Procedures for Cyanotic Congenital Heart Disease

Richard S. Ross, Melvin H. Evans, and Helen B. Taussig, Baltimore, Md.

Thirty-four patients who presented late hemodynamic complications 3 or more years after systemic-pulmonary anastomotic procedures for cyanotic congenital heart disease have been studied. The anastomosis had been constructed between the aorta and pulmonary artery in 8 of the patients and between the subclavian and pulmonary arteries in the remainder of the group. Cardiac enlargement with a cardiothoracic ratio of greater than 60 per cent was present in 16 patients, and in 8 patients this ratio exceeded 65 per cent. Congestive heart failure was present in 3 patients, and this heart failure appeared to be of the high output type resembling that seen in arteriovenous fistulas of the peripheral circulation. Massive enlargement of the pulmonary artery was present in 5 patients and was associated with chest pain and hemoptysis in 1. Pulmonary hypertension developed in 1 man with a Potts anastomosis, thus reducing the volume of shunt and causing a return of cyanosis. Autopsy evidence suggests that increasing size of the anastomosis with time may account for some of these late hemodynamic complications. It appears likely that as the age of the population with anastomotic procedures increases, these complications will be seen more frequently as the changes of aging are superimposed. It is well recognized that an anastomosis must exceed a certain minimum size if it is to be effective. It is suggested that there is also a maximum limiting value which must not be exceeded if the above-mentioned complications are to be avoided.

Patent Ductus Arteriosus in the First Year of Life: Clinical and Hemodynamic Observations in 22 Patients

Abraham M. Rudolph and Florence E. Mayer, Boston, Mass.*

Twenty-two infants with patent ductus arteriosus, aged 1 to 12 months, have been studied by cardiac catheterization and the clinical and hemodynamic data reviewed.

All patients showed poor growth and development. Thirteen had evidences of cardiac failure necessitating digitalization. Typical continuous murmurs were present in only 2 cases. There was a systolic murmur in the pulmonic area in 14, and at the apex in 6 patients. Radiologic examination revealed moderate to marked cardiomegaly and pulmonary vascular engorgement. Electrocardiographic evidence of left ventricular hypertrophy was observed in 10, combined ventricular hypertrophy in 8, and right ventricular hypertrophy in 4 patients.

At cardiac catherization, the catheter was manipulated through the ductus arteriosus in 18 cases. Pulmonary to systemic flow ratio was 2:1 in all patients, except 2 with markedly increased pulmonary vascular resistance. Additional left-to-right shunts at the atrial level were observed in 4 babies. That this may not be due to an atrial septal defect was demonstrated by the finding of a dilated foramen ovale at autopsy in 1 case, and by failure to demonstrate the atrial shunt at catheterization after ductus division in a second patient.

The pulmonary arterial mean pressure was greater than 35 mm. Hg in 16 patients. Calculated pulmonary vascular resistance was significantly elevated in 5 cases. The absence of continuous murmurs could be correlated with absence of a diastolic pressure gradient in superimposed aortic and pulmonary pressure tracings.

Twenty patients were subjected to ductus surgery. One died postoperatively, 1 expired 18 months after surgery from progressive pulmonary vascular disease, and 1 died prior to surgery.

In view of the atypical features of patent ductus arteriosus in the first year of life, this diagnosis should be considered and excluded in all infants with significant symptoms and clinical evidence of a left-to-right shunt.

Cardiac Control in Intact Dogs

Robert F. Rushmer, Dean L. Franklin, Robert W. Moss, and Allan W. Lobb, Seattle, Wash.

Changes in left ventricular pressure and dimensions in intact unanesthetized dogs provide the basic information for a continuous analysis of left ventricular performance in terms of several parameters, including: rate of change of dimensions, "power," "work," work per unit time, heart rate and rate of change of ventricular pressure. By comparison with the spontaneous left ventricular responses during changes in position, eating, and exercise with cardiovascular responses induced experimentally, the traditional technics employed for increasing cardiac output (intravenous infusions, lowered peripheral resistance) bear little relation to normal control mechanisms. The variability in ventricular responses under similar conditions in the same dog, coupled with anticipatory and conditioned reactions, are presented as evidence that "normal" cardiac control originates primarily in the central nervous system rather than in the peripheral vascular circuits.

Acute Effects of Carbon Dioxide Inhalation in Heart Failure

Joseph M. Ryan, Joseph F. Tomashefski, and Richard G. Booth, Columbus, Ohio.

Tidal, minute volume (MV), arterial pH, pCO_2 and pO_2 were determined before, during and after

5 per cent CO_2 inhalation in 7 subjects with mild to severe congestive heart failure (CHF), 4 normals and 4 emphysemas with repeat observations in 4 of the failure group following diuresis or phlebotomy. Maximal breathing (MBC) and vital capacities preceded each observation. Breathing reserve (BR) $\left[100 - \frac{MV}{MBC} \times 100\right]$ was calculated.

BRs of heart failure patients were 44, 47, 59, 60, 71, 77, and 78; of normals 84, 78, and 85; and of emphysemas 60, 69, 70, and 80. The more reduced BRs were found in the more advanced congestive failures. Those in failure with the lowest BRs experienced more dyspnea and showed more labored breathing than the normals or emphysemas. The 2 patients with the lowest BRs were restudied following diuresis. The first increased her BR from 44 to 73 and the second from 47 to 53, both showing improved tolerance to CO_2, especially the first. Following phlebotomy the third increased his BR from 59 to 67 with improved CO_2 tolerance but the fourth showed no change in either BR or CO_2 tolerance. Composition of arterial blood was similar at all sampling times in both normal and congestive failure groups but emphysemas showed consistently lower pHs and pO_2s and higher pCO_2s.

Apparently those patients with heart failure that are more dyspneic than normal or emphysematous subjects, when breathing CO_2, are so because of a greater reduction in breathing reserve at that time. In heart failure if dyspnea occurs in situations when CO_2 retention is present, resulting elevation of arterial pCO_2 may be a factor in its production. Improved breathing reserve after diuresis or phlebotomy may be of value in differentiating dyspnea due to pulmonary congestion from that due to other causes.

Measurement of Cardiac Output in the Steady State, by the Fick Principle, During Combined Right and Left Heart Catheterization

Philip Samet, William H. Bernstein, Miami Beach, Fla., Robert S. Litwak, Miami, Fla., Hyman Turkewitz, and Leonard Silverman, Miami Beach, Fla.

The development of left and combined right and left heart catheterization has permitted direct determination of the mean diastolic atrioventricular gradient in subjects with mitral stenosis, and the mean systolic ventricular-arterial gradient in patients with aortic stenosis. Quantitative evaluation of the significance of these gradients is difficult without simultaneous flow, i.e., cardiac output, determination. The purpose of this paper is to demonstrate the feasibility of such flow measurements by the Fick principle during the course of combined right and left cardiac catheterization.

Right heart catheterization was performed in the usual manner. Cardiac output was determined at rest or at rest and during exercise. The patient was then rotated into the prone position and 2 7-inch no. 17 T thin-walled styletted needles inserted into the left atrium. Polyethylene catheters were passed through the needles into the left atrium and ventricle. The needles were then removed over the catheters, leaving the latter in situ. The patient was subsequently rotated back into the supine position and flow determination repeated after a suitable rest period to permit re-establishment of the steady state.

Twenty studies have been performed in this manner in 19 subjects. The mean cardiac index, arteriovenous oxygen difference, oxygen consumption, and respiratory quotient during right heart catheterization was 2.50 L. per minute per M.², 5.2 volume per cent, 123 ml. per minute per M.², and 0.81 respectively. The corresponding values during right and left heart catheterization were 2.44 L. per minute per M.², 5.3 volume per cent, 123 ml. per minute per M.², and 0.83. The average per cent differences (disregarding the algebraic sign of the difference) were 6, 7, 6, and 6 respectively.

The corresponding data during exercise in the course of these studies were obtained 10 times in 9 patients. Although the scatter is somewhat greater than at rest (since the subject did not necessarily reach the same levels of oxygen consumption during the right heart and during the combined heart exercise periods), the agreement is again good. The mean exercise cardiac index during right heart catheterization was 3.59 L. per minute per M.², and during combined cardiac catheterization was 3.42 L. per minute per M.² The arteriovenous differences, oxygen consumption, and respiratory quotient averaged 7.6 volumes per cent, 260 ml. O_2 per minute per M.² B.S.A., and 0.87 during right heart catheterization and 7.9 volumes per cent, 258 ml. O_2 per minute per M.² B.S.A., and 0.90 during combined heart catheterization. The average per cent difference (disregarding the algebraic sign of the difference) was 6 per cent (cardiac index), 6 per cent (A-V difference), 8 per cent (oxygen consumption), and 4 per cent (respiratory quotient).

These data demonstrate the feasibility of steady state cardiac output measurements in the supine position, at rest and during exercise, in the course of combined heart catheterization.

Use of Nitrous Oxide in a New and Improved Method for Detection of Left-to-Right Shunts

Richard J. Sanders, Eugene Braunwald, and Andrew G. Morrow, Bethesda, Md.

The diagnosis of a left-to-right shunt generally depends upon the demonstration of significant differences in oxygen content among the right heart chambers. Inconclusive or misleading results are sometimes obtained with this method. A wide A-V

difference normally exists during the first minutes of N_2O inhalation. In the presence of a left-to-right shunt, left heart blood, rich in N_2O, elevates the N_2O level in the right heart, thereby making detection of the shunt possible.

Fifteen per cent N_2O is inhaled for 1 minute as integrated blood samples are drawn simultaneously from the right heart and a systemic artery. In 41 of 43 patients with proved shunts at the atrial level, the ratio of right atrial to arterial N_2O (RA/A) exceeded 30 per cent, the highest value observed in 83 control patients. In all 24 patients with proved shunts, the pulmonary artery and right ventricular ratios exceeded 20 per cent. The highest PA/A or RV/A ratios in 58 patients without shunts was 16 per cent.

The superiority of the N_2O test over the oxygen method was demonstrated in 150 patients with proved diagnoses in whom both tests were performed. Using as diagnostic criteria the N_2O ratios of 20 and 30 per cent, as described above, and an oxygen step-up of 1.5 volume per cent, there were 22 errors with oxygen differences and only 3 with N_2O.

Surgery of the Coronary Arteries: Direct Approach

Victor P. Satinsky, Eugene V. Kompaniez, Robert Kuhn, and Richard N. Baum, Los Angeles, Calif.

Direct attack on the coronary artery has been carried out experimentally and clinically in the following manner: Coronary curettage has been formed by passing an instrument through the anterior descending coronary artery and the lateral branch of the circumflex artery from a point of termination upward. A specially designed flexible probe which bears a cutting instrument on the under surface of its head, curettes the coronaries on withdrawal of this probe. This procedure has been carried out clinically with remarkably encouraging results.

Left Transventricular Approach to Aortic and Mitral Valves and to the Interventricular Septum

Victor P. Satinsky, Eugene V. Kompaniez, Robert Kuhn, and Richard N. Baum, Los Angeles, Calif.

A technic has been developed whereby the interventricular septum can be visualized and exposed for surgical attack through the left ventricle. This view also gives excellent exposure of the annulus of the aortic valve and of the mitral leaflets and chordae tendineae. An approach to the interventricular septum from the left side has the advantage of being able to repair the high interventricular septal defect without having to disrupt the tricuspid valve to gain access to such a high placed defect in the membranous portion of the septum. The easy access to the aortic annulus will find practical usage in the placement of aortic valve prostheses below coronary level. The procedure is carried out by means of the heart-lung machine; either induced cardiac arrest or retrograde perfusion may be utilized. A suture is placed in the apex of the heart after a bypass has been effected and the left ventricle lifted directly upward. An incision is made posteriorly between the branches of the coronary artery, the myocardium retracted and the residual blood in the left ventricle aspirated. A clear view of all the structures contained therein is obtainable. Following the closure of the interventricular septal defect, the myocardium is sutured in 2 layers: a running continuous suture approximating the endocardium, and mattress sutures approximating the thick muscle all itself. Care is taken to make sure that all air is expelled from the left ventricle before final closure.

Function of the A-V Conduction Tissue

Allen M. Scher, Juhan Liikane, Malcolm E. Fishback, and Leland L. Burnett, Seattle, Wash.

Multipolar needle electrodes of several types have been placed in the A-V conduction system at many sites, and records have been taken of the electric activity. Records at several sites can be taken simultaneously. The inadequacy of recording from the A-V node with a needle electrode has made it necessary to design a special 3-dimensional electrode. This electrode has a recording terminal at each millimeter on rectangular coordinates, throughout a volume of $2 \times 3 \times 6$ mm. with a total of 84 points. This 3-dimensional electrode can be inserted into the A-V node, and the current flow along each axis plotted. Positions of all electrodes are verified histologically.

Depolarization of atrial muscle near the A-V node occurs when the P wave is about two-thirds completed. The total time between this and the beginning of ventricular activity is about 50 to 60 msec. Conduction in the common bundle, and right and left bundles, accounts for all but the earliest 10 to 15 msec. of this interval. In the A-V node, there is a period of about 10 msec. when no records of cells firing are obtained, but when slow electric changes are at times found. The lack of rapid potentials is probably a function of the recording technics. Conduction velocity in the common bundle, and right and left bundles, is from 1 to 2 msec. Velocity through the A-V node often falls below 0.1 msec The term A-V delay is a misnomer, since there is probably no interval when some cells are not being depolarized. It is felt that the size and geometrical arrangement of the cells can explain the slow conduction with the node.

Vagal stimulation slows A-V conduction, largely by altering activity in the atrial cells upstream from the node. When the atria are stimulated at pro-

gressively increasing rates, conduction in the nodal region is slowed at rates of about 3 per second. Other tissues are not affected at this frequency. At faster rates, the slowing of conduction is greater. At stimulation rates of about 6 per second, atrial conduction is slowed and the A-V node may show 2–1 block. At faster rates, some slowing of conduction in the bundles is observed.

Theoretical Limitations of Vectorcardiography

Allen M. Scher and Allan C. Young, Seattle, Wash.

Vectorcardiography rests on the assumption that insofar as body surface potentials are concerned, the potentials produced on ventricular depolarization can be considered to result from a fixed intrathoracic dipole. Such a fixed dipole would be a special case of the more general situation when any 3, but only 3, current generators were each connected to separate pairs of electrodes on or within the body. If there were 3 such generators, 4 simultaneous electrocardiographic leads, A, B, C and D, would be continuously related throughout QRS by the equation $\alpha A + \beta B + \gamma C = D$, where A, B, C and D are instantaneous values of each lead and α, β and γ are constants. Once α, β and γ are determined (which requires measurement of potentials in each lead at 3 instants in time) we should be continuously able to calculate D from A, B and C. Studies of electrocardiographic leads with measurements made at 5-msec. intervals indicate that they do not fit the above equation. In control experiments D and D calculated were within 5 per cent of one another. In studies of electrocardiographic leads, D and D calculated might vary by ±150 per cent or more. Errors of up to ±150 per cent are thus inherent in the application of the fixed dipole hypothesis to ventricular depolarization.

The equations given above will define a plane in 3-dimensional space if the 3-function requirement is met. The coordinates of this space are A/D, B/D and C/D respectively. Early studies indicate that the points in 3-dimensional space determined from 4 simultaneous electrocardiographic leads tend to fall in 2 or 3 fairly well separated planes. Points in each plane are grouped in time. Should these positive findings continue, they may save vectorcardiography from the role of a useful but purely empirical tool, to which role it is relegated by not meeting the 3-function criterion.

Compatible Electrocardiographic Systems for Analysis by Conventional or by Electronic Computer Means

Otto H. Schmitt, Minneapolis, Minn.

Electrocardiography is moving rapidly toward mechanization for electronic computer analysis because the raw data is intrinsically quantitative and compact in form if redundancies are eliminated. We must therefore anticipate that in the near future much routine ECG analysis will safely be entrusted to machine measurement where accurately specifiable diagnostic criteria can be formulated. We must not assume, however, that all of the subtle items recognized by an experienced diagnostician will be programed for computer determination for some years to come, if ever. During perhaps a decade of transition, it will be desirable, moreover, to use both systems side by side until the reliability of the newer methods is proved beyond doubt. Ideally, technical means for data storage, retrieval, processing and display will be found such that the transition to machine methods can be made without any serious dislocation or the necessity for sudden drastic changes in clinical practices of recording, storing, or reading electrocardiograms.

At the present time it appears that a family of systems employing 4-channel modulation coded recording on magnetic tape promises almost all of the desired flexibility, combined with adequate accuracy and reliability, without prohibitive cost either in dollars or in re-education of personnel.

While many engineering features remain to be worked out, the proposed compatible electrocardiographic systems will certainly possess certain advantageous features. Data for standard limb leads, precordial leads, vectorial leads, resolver-reoriented spatial leads, etc., will not have to be recorded separately but will be synthesized upon demand from a single tape record costing a few cents per patient and accessible permanently for replay or re-usable in the event that the record becomes obsolete. Many recorded beats per second will be available to permit subsequent studies of arrhythmias and pathway variations. A separate channel for vocal commentaries and computer command and coding information will accompany and identify each record, making it possible to assemble desired case types automatically from a hospital library of records. Complete records for at least 100 patients would be stored on a standard reel of tape and could be played back at will onto standard single or multichannel time-based recorders, vector cardioscopes, spatial vector cardioscopes, or directly into computer analytic or diagnostic equipment.

Synthesis of the Angiotonin Octapeptide

Hans J. Schwarz, Merlin F. Bumpus, and Irvine H. Page, Cleveland, Ohio.

A biologically active decapeptide (A; X = Valyl) was isolated from the reaction mixture of renin and renin-substrate (beef). From a similar reaction using a different substrate (horse), 2 peptides were isolated, a decapeptide (A; X = isoleucyl) and an octapeptide (B). The octapeptide seems to be the biologically active form.

L-aspartyl-L-arginyl-L-valyl-L-tyrosyl-L-X-L-histidyl-L-prolyl-L-phenylalanyl-L-histidyl-L-leucine (A. Angiotonin-decapeptide or hypertensin I).

L-aspartyl-L-arginyl-L-valyl-L-tyrosyl-L-isoleucyl-L-histidyl-L-prolyl-L-phenylalanine (B. Angiotonin-octapeptide or hypertensin II).

The synthesis of the latter was achieved in our laboratory starting from 4 crystalline dipeptides, carbobenzoxy-β-methyl-L-aspartyl-nitro-L-argine, carbobenzoxy-L-valyl-L-tyrosine methyl ester, carbobenzoxy-L-isoleucyl-L-histidine methyl ester, and L-prolyl-L-phenylalanine methyl ester hydrochloride.

The final crude product was purified by countercurrent distribution and characterized by analysis of its amino acid content, R_f values and distribution coefficients.

Biologic activity and specific activity of our final, purified octapeptide were very similar to those of the angiotonin octapeptide or hypertensin II. The product was about 5 times more active than noradrenalin on the rat's blood pressure on a weight by weight basis (test arrangement as Peart). The synthetic octapeptide showed all the pharmacologic features of the natural angiotonin.

Mammary Souffle of Pregnancy

James T. Scott and Edmond A. Murphy, Baltimore, Md.

Among the growing list of causes of continuous parasternal murmurs, attention is called to that occurring during pregnancy. Two cases of this little known phenomenon are described. In 1, the continuous nature of the murmur was accentuated by light pressure with the stethoscope; in both, the murmur was abolished by firm pressure. The murmur was variable in time and situation, was unaffected by respiration, and in 1 case was heard only in the recumbent position. In the 1 patient in whom a Valsalva maneuver was tried, it increased the loudness of the murmur, but for a few beats only. Phonocardiograms confirmed these points and showed a late systolic accentuation. In both cases lactation was brief; the murmur was known to have disappeared 1 and 4 months, respectively, after delivery.

The murmur resembles that of patent ductus arteriosus, and this provisional diagnosis had been mistakenly made in 1 of the cases when the murmur was heard during a previous pregnancy.

The effect of the Valsalva maneuver and the phonocardiograms indicate an arterial origin, and the term "mammary souffle" is suggested. While some effect of pregnancy—such as breast hyperemia or engorgement, or the consequences of an elevated diaphragm—is necessary for the production of this phenomenon, some other factor, perhaps structural, may be involved, since the murmur occurs in only a minority of pregnancies and yet was observed in 2 successive pregnancies in 1 of our cases.

Timed Vectorcardiogram

Ronald H. Selvester, Donald E. Griggs, and Paul J. Smith, Los Angeles, Calif.

This is a report of a study to determine the value of recording the spatial vectorcardiographic loops along a continuous timed axis as done by Milovanovich in 1948 and by Polzer and Schuefried in 1951.

The VCG oscilloscope was photographed with a Fairchild camera, the shutter remaining open and the film moving at a constant speed. This produced a smooth, continuous tracing in which the P, QRS, and T loops were related to time in a manner similar to the conventional ECG. The first 250 subjects (75 normals and 175 abnormals) that we have studied by this method provide the basis for this report. All had conventional ECG's, spatial VCG's, chest films, and clinical evaluation. The abnormal subjects were patients studied in the cardiopulmonary laboratory of the White Memorial Hospital mainly for evaluation of congenital heart disease, with a smaller number of rheumatic, hypertensive, and luetic heart disease, and cor pulmonale.

Mean QRS, and T vectors, and QRS-T angles were plotted from the ECG's by the method of Grant and Estes. The angles of these vectors were compared to the mean vectors that were plotted from the timed VCG, using the cube system of electrode placement. With the Einthoven triangle as a reference frame in the frontal plane, 185 cases (74 per cent) showed good correlation—a mean variation of 20° or less. With the Burger triangle, good correlation was obtained in 225 cases (90 per cent); and in the horizontal plane, 218 cases (87 per cent) with the Grant and Estes system.

The single frontal-plane tracing of the timed VCG appeared to record all the information available from the 6 standard limb leads. The single horizontal-plane tracing appeared to record all the information available from the 6 precordial leads.

We believe therefore that the timed VCG combined the advantages of the graphic portrayal of the vector forces of the spatial VCG and the time relationships of the conventional ECG into a simplified graphic method.

Pulmonary Hypertension as a Complication of Chronic Left Ventricular Failure

Arthur Selzer, San Francisco, Calif.

A series of 11 cases is reported in which severe pulmonary hypertension developed as a complication of congestive cardiac failure. These 11 cases constitute 17 per cent of a series of 65 unselected cases of chronic cardiac failure in which hemodynamic studies were performed.

Chronic cardiac failure caused by overloading of the left ventricle (hypertension, coronary heart disease, aortic valve disease) leads to an elevated pressure in the pulmonary arterial system, which is a

assive transmission of high left atrial pressure due o resistance to diastolic filling of the failing left entricle. In the majority of such cases, pulmonary rteriolar resistance is normal or only slightly ele- ated. In the 11 patients included in this series, ulmonary arteriolar resistance was severely ele- ated, being in excess of 600 dynes per second per m.$^{-5}$ It is shown that the elevation of pulmonary rteriolar resistance is not related to the degree of left ventricular failure, as judged by the left atrial pressure level.

A clinical analysis of the 11 cases showed that the presence of severe pulmonary hypertension could only be suspected in 3, on the basis of physical examination, electrocardiographic, and roentgenographic findings. In none of them was pulmonary disease present, usually associated with cor pulmonale. A comparison among the 11 patients and the other cases of cardiac failure showed no significant difference in the distribution of the various etiologic factors, the duration of symptoms of cardiac failure, and the severity of clinical manifestation of failure.

It is concluded that chronic cardiac failure initiated by failure of the left ventricle may lead in a small proportion of cases to the development of pulmonary vascular disease causing pulmonary hypertension out of proportion to the degree of failure.

Serum Total Cholesterol Response to Corn Oil Feeding in Patients with Acute Coronary Occlusion

William Shapiro, E. Harvey Estes, Jr., and Helen L. Hilderman, Durham, N. C.

Fifteen patients with unequivocal evidence for acute coronary occlusion were fed corn oil supplements during the early recuperative phase and followed for 11 days or longer. One developed further myocardial necrosis, an event considered consistent with the natural history of the illness. No other adverse effects were noted.

Fourteen ate diets containing 25 to 40 Gm. of fat; 1, a 90 Gm. fat diet. Seventy grams of fresh corn oil per day emulsified in fruit juice was added to the basic diet of each. Weights remained relatively constant; activity progressed from bed rest through early ambulation.

In contrast to normal subjects, these patients showed no uniform fall in the total serum cholesterol. Control mean total cholesterol for 15 patients was 250.6 mg. per cent. After 10 to 11 and 13 to 15 days on corn oil, the values were 242.2 and 246.3 mg. per cent, respectively. Seven patients followed for 20 to 22 days on corn oil had a control mean of 241.4 mg. per cent, and after this period the mean was 239.4 mg. per cent. Five patients followed for 24 to 25 days demonstrated a mean fall of 12.7 per cent (259.2 to 226.4 mg. per cent).

Approximately equal numbers manifested tendencies for depression, no change, or actual elevation of serum total cholesterol. A patient followed 41 days exhibited a rise of 30 per cent (203 to 264 mg. per cent), while another followed 94 days dropped 25 per cent (232 to 174 mg. per cent). Rises of 64 per cent (191 to 313 mg. per cent) after 22 days, and 30 per cent (198 to 258 mg. per cent) after 15 days were recorded in 2 others.

These data indicate that the serum total cholesterol response to corn oil feeding in patients suffering the acute consequences of coronary artery disease is distinctly different from that of normals studied in this and other laboratories.

Ventilatory Mechanics in Pulmonary Edema in Man

John T. Sharp, Geraint T. Griffith, Ivan L. Bunnell, and David G. Greene, Buffalo, N. Y.*

Pulmonary compliance and resistance have been studied in 8 patients in pulmonary edema and in 7 of the 8 following recovery from pulmonary edema. Data were calculated from simultaneous measurements of esophageal pressure, tidal volume and air flow. Compliance was found to be very low in pulmonary edema, averaging .037 ± .0056 (S.E.) L. per centimeter of water or 22 per cent of the average normal value (.165 L. per cm. water). Compliance values as low as .017 L. per cm. water (10 per cent of the average normal) were encountered. Following recovery the average compliance was .089 ± .019 L. per cm. water.

Resistance was found to be markedly increased, averaging 9.9 ± .83 centimeters of water per L. per second (cm. water per L. per second) during inspiration in pulmonary edema. This value is between 3 and 4 times the normal. The average resistance following recovery was 5.3 ± 1.17 cm. water per L. per second. Resistance was consistently found to be highest early in inspiration during pulmonary edema. This high early inspiratory resistance is probably not truly resistance but rather an expression of extremely low compliance at small inflation volumes and alinearity of the static volume-pressure curve of the lung.

Other authors have shown that neither the effect of pulmonary hypertension nor the exclusion of fluid-filled alveoli from the ventilated portion of the lung explain the low compliance in pulmonary edema. The presence of bubbles of edema fluid in the alveoli or at their entrances is advanced as an important factor in producing such low compliances. The reason for this is that such bubbles would have radii of curvature substantially smaller than that of the parent alveoli; from physical considerations it can be shown that a small decrease in the effective radius of an alveolus would produce a very large decrease in its compliance.

Potassium and Digitalis Antagonism?

J. Paul Shields, D. Max Rohrbacker, and Charles Fisch, Indianapolis, Ind.

Considerable literature has accumulated on the subject of the relation of potassium and digitalis. However, the exact mode of action of potassium, when used in digitalis intoxication, remains obscure. Whether potassium antagonizes digitalis directly, or whether its action is primarily as a nonspecific myocardial depressant, is subject to conjecture.

The purpose of our study was to determine if possible the mechanism of interaction of potassium and digitalis. Our experiment was based on the assumption that "antagonism" between potassium and digitalis would become manifest by speeding of heart rate ("digitalis release") in a patient with auricular fibrillation, whose rate was controlled by digitalis when potassium was administered intravenously.

Fifteen patients with atrial fibrillation were selected from the wards of Indianapolis General Hospital. The etiology of the underlying heart disease varied. Care was taken to assure that no patient with impaired renal function was included in this study. The patients were digitalized and, to be sure that slowing of the ventricle rate was due to the myocardial effect of digitalis and not to its vagal action, 1.25 mg. atropine was administered subcutaneously. Patients who showed only a minimal increase in the ventricular rate were selected for further study. As a control, 200 ml. of normal saline was infused over a 20-minute period. This was followed with a solution containing 100 mEq. KCl per L., and 78 mEq. NaCl per L. The solution was infused at a rate of 3 to 7 ml. per minute, and the total amount of potassium did not exceed 0.5 to 0.75 mEq. per Kg. of body weight. An electrocardiogram was obtained every 5 minutes and rate was counted for 1 minute.

We failed to demonstrate the expected increase in ventricular rate. On the contrary, during the period of infusion there was slowing of the ventricular rate. Two to 4 hours after potassium infusion, an increase in heart rate was observed.

Critical Study of Existing ECG Lead Systems to Evolve one Useful Interchangeably for Scalar, for Vector, and for Electronic Computer Analysis

Ernst Simonson and Otto H. Schmitt, Minneapolis, Minn.

Eight electrocardiographic lead systems, including conventional scalar and presumably orthogonal, 3-coordinate time-parametric vector types have been studied to determine whether substantially all the important diagnostic data for any of them could be found in some one system of only 3 leads.

Work with torso models, using the transfer impedance analysis, has shown that nearly ideal orthogonal leads can be devised for homogeneous systems and that some commonly used lead systems do distort badly. The distortions are such, however, that little data is available uniquely in any one system and absent from the others.

Tests with these same lead systems on 22 normal subjects and on 50 heart patients show large divergences between different lead systems, not only in scale and relative orientation of vectorial loops, loop segments, and sense of inscription, but in intra-individual differential distortion of these differences and in response to respiratory and postural changes. These differences are so great as to be possible cause for misinterpretation and even gross error of deductions.

Despite these contraindications, really quite adequate equivalents of all the standard limb leads, the augmented limb leads, the precordial leads and all the planar vector and spatial vector leads can be easily machine-synthesized from 3 appropriate master leads.

It is our conclusion, supported by correlation and distribution studies of 200 normal men, that substantially all known important electrocardiographic data can be derived from a single set of 3 carefully chosen and simultaneously recorded leads if meticulous care is exercised in preserving phase coherency between lead components.

For convenient routine recording and storage of ECG data on tape and its subsequent recovery in any desired recorded or displayed form, such master lead recordings will suffice for any but very special cases. They will also effect enormous savings in storage space for ECG records.

This study shows that presently used lead systems are not really interchangeable and an immediate effort should be made toward marshalling all available data to permit a wise choice and standardization of 3 master leads as working standards for coming years.

Studies on the Natural History of Adrenal Regeneration

Floyd R. Skelton, New Orleans, La.

The natural history of adrenal-regeneration hypertension was studied in rats over a period of 147 days to obtain data on the interrelationships between elevated blood pressure, saline consumption, organ weights and lesions. Experimental rats died or were killed when death appeared imminent; control animals were sacrificed simultaneously and paired with them for purposes of comparison. Blood pressures above 150 mm. of Hg developed in 48 out of 50 rats bearing regenerating adrenals, but only 3 controls showed values above this level. While hypertensive rats drank more saline than did controls, no close association was found between the height of blood pressure attained and either the highest daily saline intake or the terminal weight of the regenerated

adrenal. Vascular lesions were present in rats with adrenal-regeneration hypertension regardless of duration of hypertension. Both morbidity and death of hypertensive rats were closely associated with clinical signs of brain lesions and the postmortem finding of cerebral edema, infarcts and hemorrhages.

A second experiment was done to confirm the observation that hypertension can persist following removal of the regenerated adrenal and to study the frequency of this occurrence. Rats with severe adrenal-regeneration hypertension were completely adrenalectomized and maintained on saline. Following adrenalectomy, 13 rats died within the first week, 10 of which remained hypertensive; 11 died between the first and fifth week, all of which remained hypertensive; 19 survived for 5 weeks, and of these 17 were severely hypertensive.

Based on these studies the development of hypertensive vascular disease in rats with regenerating adrenals cannot be totally attributed to an increase in saline consumption. Eventually this hypertension becomes independent of the regenerated adrenal since adrenalectomy is followed by a significant fall in blood pressure in only a small percentage of animals.

Effect of Group A Streptococci and Components of the Cell on Adrenalectomized Rats

Hutton D. Slade† and Yoshitami Kimura, Chicago, Ill.

The toxic substances produced by the group A streptococcus and their effects on laboratory animals have long been a subject of interest. To obtain information on this subject we have investigated the effect of the group A streptococcal cell and several purified components of the cell in the adrenalectomized rat.

Normal rats are highly resistant to infection by the group A streptococcus. Suspensions containing 38×10^{10} cells (type 19) have been injected intraperitoneally without clinical symptoms. The liver, spleen and lymph nodes of these animals, in the great majority of cases, gave a negative culture for *Streptococcus pyogenes*. Adrenalectomized rats, however, died within 24 hours, following an intraperitoneal injection of 4.8×10^{10} cells. The liver, spleen and lymph nodes were uniformly positive when cultured for the group A streptococcus. Pretreatment of the rats with cortisone completely protected against the streptococcal infection. The antihistamine pyribenzamine had no protective effect. A 4-fold dose of a group D streptococcus caused no deaths, whereas the same dose of *Staphylococcus aureus* caused the death of approximately 50 per cent (3 of 5) of the rats.

Heat-killed group A streptococci were also lethal for adrenalectomized rats. However, approximately 8 times (2.1 mg.) as many organisms were required to kill as compared to living cells. This finding indicated that a component of the streptococcal cell was responsible in part for the toxic effect.

Highly purified type-specific M protein was prepared by extraction and chemical fractionation of type 6 and 19 organisms. Two milligrams of either preparation upon intravenous injection caused death within 5 minutes. The histamine content of the organs of these rats, as measured by kymograph, was about 10 times that of untreated rats. No effects were observed when M protein was injected into normal rats. A purified component devoid of M protein obtained by chemical fractionation of a type 19 streptococcus did not cause death. These results demonstrate that a component of the group A streptococcus, the M protein, is highly toxic to the adrenalectomized rat. Other components of the cell are under investigation.

Screening Test for Renal and Adrenal Forms of Hypertension Based Upon Postural Change in Blood Pressure

Reginald H. Smithwick, Dera Kinsey, and George P. Whitelaw, Boston, Mass.

This paper deals with a simple screening test as an aid in the differentiation of etiologic factors in hypertension. Recently more attention is being focused upon methods of selecting cases of hypertension based on humoral factors, namely, adrenal and renal mechanisms. It is generally agreed that cases of this type are relatively rare in comparison to those of the so-called neurogenic or essential variety. It is, however, extremely important to make an accurate diagnosis as the therapy for cases of hypertension with a humoral mechanism as the primary factor is so extremely satisfactory.

In 1950, Smithwick, Greer, Robertson, and Wilkins pointed out that cases of humoral hypertension from pheochromocytoma showed a drop in systolic and diastolic levels in a high percentage of cases when changing from a horizontal to a vertical position. Our experience in dealing with cases of pheochromocytoma since this time has confirmed this finding and, in addition, cases of humoral hypertension resulting from unilateral kidney disease and primary aldosteronism often appear to behave in a similar fashion.

The data in this paper is presented as a result of postural blood pressure tests being done on 28 patients with renal or adrenal hypertension and compared to the blood pressure responses in 100 unselected patients with hypertension studied prior to the use of hypotensive agents. Six of the 28 patients had hypertension due to unilateral kidney disease, 4 had hypertension in association with primary hyperaldosteronism, while 18 patients had hypertension due to pheochromocytoma. No patient with Cushing syndrome is included in this study as postural tests were not done on a sufficient number of these cases to evaluate the postural changes that

occur when hypertension is in association with Cushing's disease.

Fifty-six per cent of the unselected patients studied with hypertension showed an increase in systolic pressure while standing, while none of the 28 patients with hypertension of adrenal or renal origin showed an increase in systolic pressure when changing from a horizontal to a vertical position. Forty-one per cent of the unselected group of hypertensive patients, however, showed a fall in systolic pressure when standing, while 93 per cent of the patients with renal or adrenal hypertension showed a fall in systolic pressure when changing from the horizontal to the vertical position.

We feel this is a simple and effective screening test that can be carried out as an office procedure and be a valuable aid in pointing toward more detailed studies that would be necessary for differentiating cases of hypertension based on renal or adrenal factors from those of the so-called essential or neurogenic group.

Kyphoscoliotic Cardiopulmonary Disease: A Reappraisal

Gordon L. Snider, George Miller, Bernard Miller, and Edward I. Elisberg, Chicago, Ill.

It has been common teaching for many years that severe kyphoscoliosis results in cardiac failure and death usually in the fourth or fifth decade of life. Twenty-six cases of severe skeletal deformities of the chest have been studied in an attempt to re-evaluate the association of cardiopulmonary disease with this condition. The patients ranged in age from 6 to 71 years; they were evaluated by means of history, physical examination, pulmonary function tests, roentgenologic examination, and electrocardiograms. Six patients underwent right heart catheterization.

These cases can be divided into 3 groups on the basis of physiologic findings. All patients demonstrated evidence of a severe restrictive ventilatory defect. Patients in group I have only this defect; they have no cardiorespiratory symptoms. Patients in group II give a history of recurrent bronchitis and have evidence of some degree of airway obstruction combined with their restrictive ventilatory defect. However, in the intervals between episodes of bronchitis, symptoms are minimal or absent. In patients of group III the airway obstruction is much greater in severity and there is evidence of chronic diffuse obstructive emphysema. Pulmonary hypertension at rest or on exercise is present and polycythemia and congestive cardiac failure may complete the picture of chronic cor pulmonale.

Patients may progress through the 3 stages of the condition and die from cor pulmonale and pulmonary insufficiency or may remain indefinitely in one of these stages. An understanding of the underlying pulmonary disease is the keynote in the treatment of cardiac failure complicating kyphoscoliosis.

The possible mechanisms resulting in the development of chronic diffuse obstructive emphysema and a plan for the management of these patients will be discussed.

Size of the Pulmonary Artery in Rheumatic Heart Disease with Mitral Stenosis and its Significance

Louis A. Soloff, Jacob Zatuchni, George E. Mark, Jr., and Herbert M. Stauffer, Philadelphia, Pa.

A study was made of 25 consecutive persons with rheumatic heart disease and mitral stenosis by the combined technic of cardiac catheterization and biplane stereoscopic venous angiocardiography to determine the diameter of the pulmonary artery and its relationship to pulmonary artery and capillary venous pressures, to pulmonary vascular resistance, to left atrial volume, to the frontal area of the heart, to the diameter of the aorta, and to age.

The diameter of the aorta varied from 19 to 45 mm. (average 33 mm.) and that of the pulmonary artery from 28 to 50 mm. (average 37 mm.). The diameter of the pulmonary artery exceeded that of the aorta in 20 of the 25 subjects. The diameter of the pulmonary artery showed no correlation with left atrial volume ($r = 0.194$), a low grade one with heart size ($r = 0.317$) and with age ($r = 0.387$), and a fair correlation with pulmonary vascular resistance ($r = 0.55$) and with mean pulmonary capillary venous pressure ($r = 0.51$). The relationship was better with the difference between the mean pulmonary artery and capillary venous pressures ($r = 0.722$), and best with the mean pulmonary artery pressure alone ($r = 0.765$).

It is concluded that in rheumatic heart disease with mitral stenosis, the aorta is usually decreased in size relative to that of the pulmonary artery, and that the size of the pulmonary artery is related best to the mean pulmonary artery pressure and not at all to left atrial volume. Although higher pressures are seen with larger pulmonary arteries, nevertheless, for any given size of the pulmonary artery, one may expect a wide variation of values of mean pulmonary artery pressures ($\Sigma = 10.7$).

Evaluation of Estrogen Therapy in Males with Previous Myocardial Infarction: Interim Report—Four-Year Follow-Up

Jeremiah Stamler,† Ruth Pick, Louis N. Katz, Benjamin Kaplan, and Alfred Pick, Chicago, Ill.

In late 1952, a long-term study was instituted on the possible efficacy of sustained estrogen therapy in males with previous myocardial infarction. This report presents data on those patients under observation for approximately 4 years. Detailed precautions were instituted from the onset to assure proper design, with matching of the placebo and estrogen groups, minimizing of bias, and effective

handling of the multiple problems of control arising during the course of such an investigation.

A total of 37 placebo and 57 estrogen patients entered the study prior to June 1, 1954. As of June 1, 1957, mean duration of follow-up on study was 44.2 and 44.5 months respectively; mean duration since first infarct, 53.2 and 52.4 months. The dosage schedule was gradually increased from 1.25 or 2.5 to 4.0 to 10.0 mg. of oral mixed conjugated equine estrogens daily, leading to sustained gynecomastia, depression of libido and potency, without toxic effects. Anticipated alterations in serum lipid-lipoprotein levels occurred and were sustained. Continuous follow-up data are available on 33 placebo and 36 estrogen patients (89 per cent and 63 per cent respectively of the original groups).

Of these, 8 placebo and 3 treated patients died due to coronary disease. The study is continuing with the follow-up of larger groups of patients (78 and 98) who at present have been under observation for shorter periods (less than 3 years).

Continuous Pressure Differences Across Stenotic Mitral and Aortic Valves Recorded During Left Heart Catheterization

Leonard E. Steinfeld, Paul A. Kirschner, James B. Minor, Leslie A. Kuhn, and Alvin J. Gordon, New York, N. Y.

Simultaneous equisensitive pressure pulses have been recorded in the left atrium, left ventricle, and aorta. The ascending aorta is catheterized in retrograde fashion from the brachial artery; the other two chambers are entered transbronchially. By the method previously described, in the heart exposed at operation the three pulses are displayed and photographed on the same scale and with the same base line. In addition, a new 8-channel oscilloscopic recorder permits simultaneous registration of the electrocardiogram, heart sounds from 2 different points on the chest, and continuous pressure differences across the aortic and mitral valves. The latter are derived by electric subtraction of the outputs of the 2 pairs of pressure transducers involved.

The continuous pressure difference during diastole across the stenotic mitral valve (filling pressure gradient) is characteristically M-shaped; that across the stenotic aortic valve during systole (ejection gradient) has the shape of an inverted V. Good correlation exists between these pressure differences and the intensity of the simultaneously recorded murmurs.

"Silent Coronary": An Analysis of the Factors Associated with Clinically Unrecognized Myocardial Infarctions

Joseph Stokes III and Thomas R. Dawber, Framingham, Mass.

Five thousand two hundred and nine residents of Framingham, Mass., between the ages of 30 and 59, received a complete cardiovascular examination, including a 12-lead electrocardiogram, between October 1948, and June 1952. Subsequently, most of these subjects returned for repeat examinations, including serial electrocardiograms, every 2 years during a period of follow-up varying from 5 to 9 years.

During this period, 67 individuals developed definite electrocardiographic evidence of myocardial infarction. At the time of the initial examination, some of these subjects had angina pectoris or other clinical evidence of coronary artery disease. Only those persons with electrocardiographic evidence of a myocardial infarction were excluded from the study.

Of the 67 individuals who developed myocardial infarctions, 50 (75 per cent), had illnesses which were clinically recognized as coronary attacks, most of which were electrocardiographically confirmed at the time of the illness, but 6 (9 per cent), denied any symptoms whatsoever, and 11 (16 per cent), had chest or abdominal pain or other symptoms, and signs of varying degrees of severity which were not interpreted by the patient or the attending physician as manifestations of myocardial infarction.

The clinical characteristics of the 17 individuals with unrecognized myocardial infarctions were then compared with those of the 50 subjects with recognized infarcts, in order to identify any unique manifestations of the "silent coronary."

It was determined that anterolateral myocardial infarction was more common in the recognized group, 11 (22 per cent), than in the unrecognized group, 1 (6 per cent), and that the incidence of angina pectoris following the attack was significantly higher in the recognized group as compared with the unrecognized infarcts. However, there were no significant differences between the 2 groups when analyzed regarding age, occupation, weight, blood pressure, and heart size.

It can be concluded, therefore, that a significant proportion of myocardial infarctions are clinically unrecognized, and that the "silent coronary" most commonly is posterior or anteroseptal in position and is less commonly followed by angina pectoris than are recognized infarcts.

Water Metabolism after Cardiac Operations Involving Extracorporeal Circulation

George S. Sturtz, John W. Kirklin, Edmund C. Burke, and Marschelle H. Power, Rochester, Minn.

Postoperative water metabolism was studied in 21 children who had undergone cardiac operations involving extracorporeal circulation with the Gibbon-type pump oxygenator. An intracardiac defect was repaired in each case; potassium asystole was used in 18 of the 21 cases. Each patient was studied for the first 72 hours postoperatively.

The daily body weight, water input, urine output,

abnormal losses, insensible water loss, serum and urine osmolalities, obligatory and free urine water volumes, and the daily urine solute excretion were measured or calculated for each 24-hour period. An attempt also was made to calculate the water of oxidation and the preformed water.

The urine solute excretion averaged 294, 465, and 548 M-osm. per M.² per day for the first, second and third days, respectively. These values are much higher than expected; this may be due to the tissue breakdown associated with the operation or to improvement in the patient's cardiac status.

Water input was predominantly intravenous; no electrolyte was given to any patient during the course of the study. Water input varied between 450 and 1,000 ml. per M.² per day.

The insensible water loss averaged 469, 420, and 321 ml. per M.² per day on the first, second, and third days, respectively. These values are less than half the average values found by Talbot. Each patient was in an oxygen tent filled with water mist generated by 2 Mist-O_2-Gen units. It is presumed that the small insensible loss of water was due to a decreased loss of water via the lung; the decreased pulmonary water loss presumably was due to the increased water content of the tent atmosphere.

The urine water concentration had an average minimal value of about 1.0 ml. per M-osm. in most patients; exceptions were those who received a mild water load on the third day of observation. One milliliter of water was assumed to represent the obligatory water needed for excretion of 1 M-osm. of urine solute. Thus, very little free urine water was found at any time except in those patients who were moderately water loaded on the third day.

Serum water concentrations were determined in each patient as often as was practical. Poor correlation was noted between the water balance data and the serum water concentration. Some patients who were in negative water balance daily had a progressively increasing serum water concentration. Conversely, some patients in marked positive water balance had persistently low serum water contents. Serum water concentration was found to be of little value as an objective measure of the state of hydration in this group of patients.

A simple equation was derived for calculation of the average obligatory water losses. The answer obtained by substituting in the equation the data for a given day was presumed to represent a reasonable estimate of a patient's water need for that particular day. Five hundred milliliters per square meter per day was the average amount needed to maintain water balance during the first postoperative day; 600 ml. per M.² per day was the average amount needed to maintain water balance on the second and third days. These values are much lower than any estimates of postoperative water need found in the literature.

The daily change in body weight correlated well with the balance data; it substantiated our impression that these patients were receiving sufficient water. The daily body weights represented the simplest, most nearly accurate, and most informative data that were collected in this study. Provided the body weight is measured daily, it is possible to manage water balance adequately in the usual patient after extracorporeal circulation without such measurements as serum and urine osmolalities, urine solute excretion and insensible water loss.

Effect of Potassium and Calcium Deficiency on Ectopic Beats

Borys Surawicz, Victor Kaljot, Burlington, Vt., Murdo G. MacDonald, Montpelier, Vt., Eugene Lepeschkin,† Burlington, Vt., John C. Bettinger, and Arthur Bickford, Philadelphia, Pa.

Spontaneous supraventricular and ventricular ectopic beats and rhythms appeared in isolated rabbit hearts after 0.3 to 3 minute of perfusion with potassium-free Krebs-Henseleit solution. The appearance of ectopic beats coincided with increased steepness of the plateau and lengthening and flattening of the descending limb of the monophasic action potential. No ectopic beats appeared during perfusion with potassium-free and calcium-free solution. Ventricular fibrillation produced by perfusion with potassium-free solution was sometimes abolished by removal of calcium from the perfusing solution.

These observations prompted a clinical investigation of the effect of induced hypocalcemia on ectopic beats in humans. Edathamil disodium, 2.0 to 3.5 (average 2.9) Gm. of 10 per cent solution in saline, were infused intravenously within 8 to 40 (average 18) minutes in 25 patients with either multiple ectopic beats or stable ectopic rhythms under electrocardiographic control. The method proved safe. Serum calcium decreased after infusion from 0.8 to 1.9 (average 1.37) mEq. while serum sodium, potassium, and blood pH were not significantly altered. All or nearly all ventricular ectopic beats disappeared in 9 out of 18 patients. All supraventricular ectopic beats disappeared in 7 out of 13 patients. Atrial fibrillation was not affected. The disappearance of ectopic beats had no constant relation to a change in heart rate. Results in patients receiving and not receiving digitalis were similar.

In several cases the coupling interval of the ventricular premature beats become progressively longer as the Q-T interval lengthened during infusion of edathamil disodium. This was attributed to prolongation of the refractory period which may constitute the mechanism responsible for suppression of the ectopic beats by means of calcium deficiency.

Induced alterations of calcium/potassium ratio in blood may assume practical value in therapy of cardiac arrhythmias.

Diagnostic Applications of Indicator Dilution Technics in Congenital and Acquired Heart Disease

H. J. C. Swan and Earl H. Wood, Rochester, Minn.

Since the introduction of continuously recorded dilution curves in systemic arterial blood for diagnosis of cardiovascular abnormalities in 1950, many special applications of the technic have been developed, particularly in conjunction with right heart, left heart and arterial catheterization. These technics utilize multiple injection sites and simultaneous recording of dilution curves at multiple sampling sites in the heart and great vessels. Both injection and sampling sites are selected so as to allow the best possible demonstration or localization of the particular abnormality in question. The special applications are based both on the fundamental contours previously described as characterizing the circulatory abnormalities associated with venoarterial and arteriovenous shunts, valvular insufficiency or congestive failure as well as on the similarity or dissimilarity of dilution curves obtained following injection or recording of indicator at different sites selected specifically so as to supply critical information in regard to the diagnostic problem under consideration. Many of these applications, such as the localization of a right-to-left shunt, the identification of a central arterial vessel, or the demonstration of a left-to-right shunt from the left ventricle in addition to a shunt at atrial level, have been in use in conjunction with the right heart catheterization procedures for a number of years. Others, particularly those concerned with the localization of valvular insufficiency, have been applied since the introduction of the technic of combined aortic and right and left heart catheterizations. The routine application of dilution technics based on the principles outlined above has so greatly facilitated the precise diagnosis of cardiac disorders, both congenital and acquired, that these technics are now regarded as an almost indispensable part of the hemodynamic study of cardiac patients in our laboratory.

Evaluation of the Surgical Treatment of Patients with Coexisting Atrial Septal Defect and Pulmonary Valvular Stenosis

Henry Swan and S. Gilbert Blount, Jr., Denver, Colo.

Fifteen patients with valvular pulmonary stenosis and a defect of the atrial septum have been studied prior to and following surgery.

Patients with mild valvular stenosis and a defect in the atrial septum develop increasing left to right shunts and cardiac enlargement, often with congestive failure following relief of the valvular stenosis without closure of the atrial septal defect. Patients with severe valvular stenosis and right to left shunts prior to surgery, in general, continue to demonstrate cyanosis and peripheral arterial unsaturation following relief of the valvular pulmonic stenosis only.

The last 4 patients in this series have been cured by a single operation during hypothermia. Open repair of the pulmonary valve is first performed. After a few minutes, a second circulatory occlusion allows suture closure of the atrial septal defect. This experience has lead to the conviction that both relief of stenosis and closure of the atrial septal defect at the same operation is the only certain method to effect the cure of these patients.

Coronary Profile: Approach to the Early Diagnosis of Coronary Atherosclerosis

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Clinical evaluation of patients today by routine cardiac examination is inadequate in determining coronary atherosclerosis. The coronary profile is an approach to the early diagnosis of this condition. It is composed of a series of examinations: history and physical, blood lipids, resting and stress electrocardiograms, and cardiac x-rays. These factors are graded into a profile and each abnormality is then numerically evaluated according to normals established over a 4-year period for males ages 15 to 70. The final total grade places the patients into 1 of 3 zones, designated as green, yellow, and red, and predicated upon the integrity of the cardiovascular system and the immediacy of clinical coronary abnormalities. The red zone patients are thought to represent individuals with significant coronary atherosclerosis, and a predicted future of imminent coronary abnormality if they remain untreated. Results on 175 males, ages 15 to 70, over a 4-year period up to the present date, have indicated that in such an approach, considering an inclusive evaluation, all of these factors have statistical merit in accomplishing the goal of early diagnosis of coronary atherosclerosis. Comment is made on the relationship of cholesterol to other blood lipids, and its validity as an indicator of all blood lipids. This study was part of the initial work performed on normal subjects and those with proven myocardial infarctions to determine the scoring system indicated for blood lipids in the coronary profile. One hundred seventy-five patients, all untreated, are presented. These patients have been followed for a period of 2 to 4 years, and a statistical analysis made of the results of prediction. Red zone patients had coronary abnormalities approximately 9 times higher than green zone patients, and these results are believed to be statistically valid.

The coronary profile system is applicable to com-

munity practice because of the relative simplicity of equipment needed and the technics used.

It is believed by the authors that an inclusive evaluation of the physical, chemical, radiographic and electric factors of a patient's coronary status has a promising potential, in the form of the coronary profile, for the early diagnosis of coronary atherosclerosis.

Nodular Panniculitis after Massive Prednisone Therapy for Rheumatic Fever in Children

Angelo Taranta, Irvington, N. Y., Herbert Mark, White Plains, N. Y., Raymond C. Haas, Irvington, N. Y., and Norman S. Cooper, New York, N. Y.

The recurrence of symptoms and signs of disease activity at the end of therapy in rheumatic fever has been known for the last 75 years. This phenomenon has attracted considerable attention since steroid hormones were introduced in the treatment of rheumatic fever. It has been pointed out that the disease activity following discontinuation of treatment is often of higher degree than would be expected at that time if the disease had been allowed to follow its natural course. Recently, we have observed instances in which, at the end of massive prednisone therapy, a syndrome occurred which was not present before treatment and which is distinct from rheumatic fever. Furthermore, we have observed that this syndrome, which followed prednisone administration, apparently can be treated by cautious further administration of the same drug.

Six episodes of nodular panniculitis following cessation of massive prednisone therapy have been observed in 3 patients over a 6-month period. The total amount of prednisone received ranged from 3,140 to 5,649 mg., and the duration of therapy from 79 to 146 days. The time interval between the end of therapy and first detection of the nodules ranged from 1 to 13 days. In 2 patients these episodes of nodular panniculitis were self-limited and systemic symptoms and signs were only mild. In the third patient severe constitutional symptoms and signs were observed. These were controlled, and the subcutaneous nodules made to disappear, by further administration of prednisone. This sequence of events repeated itself twice.

Five biopsies of subcutaneous nodules were performed. Histologic sections demonstrated various degrees of inflammation of the adipose tissue and of fat necrosis.

The clinical implications of these findings and their relationship to known forms of panniculitis and to other complications and sequelae of steroid administration will be briefly discussed.

Experiments on Prophylactic Digitalization in Pulmonary Edema and Acute Heart Failure

Mario R. Testelli, John F. Polli, and Seymour B. Musiker, Chicago, Ill.

Experiments have been made in 180 rabbits and 108 rats in order to investigate the possible effects of preventive and therapeutic digitalization in acute pulmonary edema. Three methods have been used for inducing pulmonary edema: (a) i.v. epinephrine (rabbits); (b) i.v. chloroform (rabbits); (c) inhalation of chlorine gas (rats).

Digitalization was prophylactic in certain groups and therapeutic in others. Prophylactic treatment was done by parenteral administration of digitoxin for 9 days, 3 days, or in a single dose 30 minutes before provoking the attack. Therapeutic treatment was done at the same time, 2 minutes after provoking the attack, or 30 minutes later. Drugs used for digitalization were: digitoxin, ouabain, and acetylstrophanthidin. The experiments indicated that digitalization was not beneficial.

Use of Coronary Arteriography in Human Coronary Sclerosis

Alan P. Thal,† Richard G. Lester, L. Stephen Richards, and M. John Murray, Minneapolis, Minn.

Great advances in precise diagnosis and definitive therapy have followed the development of cerebral arteriography, aortography, and arteriography of the extremities. The blood vessels of the heart, however, have not yet been studied in coronary sclerosis of the living human, although coronary arteriograms have been obtained incidental to retrograde aortography. The present study will outline the technics which have been used in applying arteriography successfully in several cases of advanced arteriosclerotic cardiovascular disease. The application of this work to precise diagnosis and possibly to surgical therapy will be discussed. At the time of writing this abstract, coronary arteriograms have been performed on over 20 patients, ranging in age from 17 to 76 years. The last 10 of these patients have had coronary sclerosis of varying degrees.

The procedure is done under local anesthesia, using a large malleable cardiac catheter which is maneuvered through the brachial artery into the ascending aorta under fluoroscopic vision. Experiences with various radio opaque media will be described. The opaque medium is rapidly injected within about 1½ seconds, using a pressure injection device. The carotid arteries are compressed during the injection to minimize circulation of opaque medium into the brain.

Several representative cases will be demonstrated showing various types of sclerotic, and occluding coronary lesions, including cases of senile ectasia,

hypertensive cardiovascular disease, and stenosis of the anterior descending and right coronary arteries. Cases of complete occlusion of the anterior descending and circumflex arteries and details of the collateral circulation will be shown. Electrocardiograms taken during the injection of opaque media show only slight bradycardia, which is probably a reflection of carotid sinus compression. Apart from a transient feeling of warmth, even those patients with advanced coronary disease have shown no other sequelae. These preliminary studies suggest that the method holds promise for both diagnosis and prognosis in difficult clinical cases of arteriosclerotic heart disease.

Cardiovascular Case Finding in an Oklahoma County Using 70 mm. Photofluorographic Films

William B. Thompson and Kirk T. Mosley, Oklahoma City, Okla.

The purpose of this study was to determine the practicability of reviewing the photofluorographic films for cardiovascular disease in a general population group, not only to determine previously undiagnosed individuals but also those who would benefit from medical and rehabilitation care.

The Oklahoma State Heart Association and the Oklahoma State Health Department surveyed a typical Oklahoma county. Fourteen thousand four hundred and sixty-five films were reviewed by a radiologist and a cardiologist. One thousand two hundred and seventy cardiovascular abnormalities were found. Questionnaires were returned by the local physician; a review team re-evaluated the films returned by the local physicians as not showing pathology as well as those unreported by the physicians.

Detailed statistical data regarding etiological groups, age, sex, race, physical findings, type of rehabilitation needed, as well as the relationship of graduation date of the local physician to the use of laboratory aids, completeness of report, rehabilitation requests, and cooperation, are available. Postgraduated education need may possibly be determined.

The practical problems of follow-up, diagnostic facilities, medical referral, patient and doctor cooperation, iatrogenic disease, monetary cost, and acceptance by medical as well as lay population are considered.

Congestive Heart Failure: Serial Blood Ammonia in Relation to Hepatic Function and Ammonium Chloride Therapy

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Chronic congestive heart failure is occasionally associated with lethargy, confusion and disorientation, sensorial disorders that are unexplained by the available studies of cerebral hemodynamics and metabolism. The occurrence of hepatic insufficiency in patients with congestive heart failure is generally accepted. Previous observations from this clinic led to the suggestion that ammonia intoxication might be responsible for this encephalopathy, secondary to the hepatic insufficiency, the disturbance being precipitated or aggravated by exogenous ammonia supplied by ammonium chloride therapy.

In an effort to define the possible role of abnormal ammonia metabolism in cardiac decompensation, the following data were gathered serially (periods up to 4 weeks) in 6 patients prior to, during, and following therapy for advanced chronic right heart failure: arterial blood ammonia, liver function battery, serum electrolytes, and serum glutamic oxalacetic transaminase. Patients were observed for any change in behavior or sensorium. Following a control period each patient was treated with increasing oral doses of ammonium chloride up to 12 Gm. per day, as mercurial diuretics and acetazolamide were administered intermittently.

The arterial blood ammonia was abnormally elevated in 3 of the 6 patients prior to treatment. There was no significant rise in serial ammonia determinations in any of the patients while receiving increasing amounts of ammonium chloride. In spite of good diuresis in all patients, there was no decrease in blood ammonia in the 3 patients with elevated control levels. Sporadic lethargy or mild confusion appeared in several instances, but was not related to increased blood ammonia. The pattern of hepatic function showed a tendency for bromsulfalein retention to decrease as cardiac compensation was restored, but did not parallel the blood ammonia levels. Serial glutamic oxalacetic transaminase did not change significantly.

On the basis of these observations, it is apparent that arterial hyperammonemia did not correlate with the sensorial changes or hepatic functional patterns and, furthermore, was not aggravated by the oral administration of ammonium chloride in doses up to 12 Gm. per day.

Tricuspid Regurgitation Masquerading as Mitral Regurgitation in Patients with "Pure" Mitral Stenosis

Joseph Uricchio, Harry Goldberg, and William Likoff, Philadelphia, Pa.

The presence of a loud systolic murmur at the apex of the heart in patients with mitral stenosis is generally ascribed to coexisting mitral regurgitation. However, 6 patients are presented in whom this auscultatory finding was caused by tricuspid regurgitation.

In 3 of these patients, combined right and left heart catheterization revealed marked pulmonary

hypertension, diminished cardiac output, and increased pressure gradient across the mitral valve during ventricular filling. Mitral valve areas were significantly reduced. The remaining 3 cases were studied by the technic of cardiac ventriculography. Opacification of each ventricle was accomplished by the direct injection of radio opaque dye via a subxiphoid approach. Serial films, taken at rapid intervals, revealed tricuspid regurgitation (immediate opacification of the right atrium, but no mitral regurgitation (no opacification of the left atrium).

These experiences imply that the murmur of tricuspid regurgitation may simulate that heard in mitral regurgitation. Furthermore, it may be heard at an area in which the murmur of mitral regurgitation is generally recognized. Hence, the differentiation between these valve defects becomes most difficult and may require precise diagnostic technics. Ventriculography and catheterization of the left heart have proven very helpful in this regard.

The need to identify which of the valve defects is responsible for the apical systolic murmur may be a matter of great importance, especially if mitral commissurotomy is denied on the supposition that the systolic apical murmur represents dynamic mitral insufficiency. This required particular emphasis, because tricuspid regurgitation which masquerades as mitral regurgitation apparently occurs in common association with a high degree of "pure" mitral obstruction.

Drop Meter: A Simple Device for Measuring Coronary Artery Flow

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In the beating dog's heart, the proximal and distal ends of the anterior descending artery are cannulated in such a way that the circuit of coronary flow is maintained through 2 polyethylene catheters joined together by a drop chamber. A simple photoelectric cell system counts the drops as they enter the drop chamber. Thus the rate of coronary flow, with intact peripheral resistance, is indicated by the number of drops per minute. This rate is electronically recorded simultaneously with the systemic blood pressure and electrocardiogram. The volume of flow can readily be calculated by measuring the number of drops per milliliter.

With this simple new technic, which is free of moving parts, it is demonstrated that the coronary flow is decreased by most cardiac arrhythmias, and that the coronary flow varies proportionately with the systemic blood pressure. Simultaneous comparative measurements with the drop meter and the rotameter suggest that the latter instrument is subject to gross error.

Coronary and Peripheral Bloodflow Following Hemorrhagic Shock, Transfusion, and Norepinephrine

Keith D. J. Vowles, Cecil M. Couves, and John M. Howard, Atlanta, Ga.

Clinical and experimental evidence now suggests that myocardial depression is an important factor in the development of irreversibility in hemorrhagic shock.

In an experimental study based on the Fine shock preparation, using anesthetised dogs, the coronary sinus and femoral vein were cannulated so that with the intermittent tightening of a ligature the blood flow could be deviated through a small exteriorized cannula, the flow in the coronary sinus or femoral vein thus being measured directly for a period of 30 seconds.

In acute hemorrhagic shock, the mean coronary sinus outflow fell to half its control level despite an equal fall in coronary resistance and a marked peripheral vasoconstriction. Blood transfusion, both in early and late phases, even in amounts falling far short of that necessary to produce normovolemia, restored both coronary and peripheral flow and resistance to rates approaching normal.

Norepinephrine, both in the early and late stages of shock (although more markedly in the acute phase), increased coronary flow far above the control rate. There was a corresponding decrease in coronary resistance, and the peripheral vasoconstriction was maintained. The changes in the coronary circulation with norepinephrine represent an exaggeration of its normal response to shock and may be of benefit to the myocardium. These findings lend support to the concept that, particularly in the geriatric group, norepinephrine might temporarily protect the heart of the hypotensive patient while steps are taken to correct the basic defect.

T Wave Alternans: Electrocardiographic Sign of Heart Failure

James R. Warbasse and Harold H. Dodge, Durham, N. C.

Electric properties of the heart as recorded in clinical electrocardiography are ordinarily considered to give little information concerning mechanical features of heart function. Others have previously noted that pulsus alternans may be associated with alternation of the T waves and that pulsus alternans is not an uncommon manifestation of heart failure. In patients with pulsus alternans, alternation becomes more marked or more apparent following premature contractions, particularly when the patient is tilted head-up.

This is a study of postextrasystolic T wave alternans. In 26 patients with premature contractions, simultaneous electrocardiograms were recorded

with the patient flat and tilted head-up 60°. Thirteen patients had postextrasystolic alternation of the T waves that persisted for 3 or more beats. Thirteen did not show T-alternation. The T wave alternation was invariably associated with postextrasystolic pulsus alternans and was seen only in patients with clinical evidence of heart failure. Although less common than postextrasystolic pulsus alternans, persistent pulsus alternans may also be associated with T wave alternans. The 13 subjects that did not show T alternation had neither postextrasystolic pulsus alternans (alternation in pulse pressure amplitude for 3 or more beats) nor heart failure.

The T wave variations were characterized by alternate changes in the amplitude and/or direction of the mean T vector and duration of QT interval. These T changes were not associated with alternate QRS changes. The absence of QRS changes is evidence that the alternate T wave variations reflect a "primary" change in repolarization, probably as a consequence of the beat-to-beat changes in heart size and intraventricular tension of pulsus alternans. This lack of alternation of the QRS complex lends no support to previous theories that pulsus alternans is caused by alternate variations in ventricular depolarization and that T wave changes are a secondary phenomena. The clinical significance of this study is that T wave alternans is a sign of pulsus alternans and heart failure.

Back-flow in the Aorta of Patients with Aortic Insufficiency Studied with an Indicator Technic

Homer R. Warner and Alan F. Toronto, Salt Lake City, Utah.

A method has been developed which permits the calculation of the time course of back-flow velocity in the descending aorta of patients with aortic insufficiency. Instantaneous back-velocities in excess of 100 cm. per second have been observed. An oscillation in the velocity curve during diastole has been demonstrated with this technic.

The method involves the simultaneous measurement of the time course of Evans blue dye concentration in left radial and femoral artery blood following injection into the descending aorta at various points in time and space. Via the right femoral artery, an arterial catheter is advanced until its tip lies in the aorta near the origin of the left subclavian artery. Dye solution, 0.15 ml. (2.25 mg.), is injected through the catheter under 100 p.s.i. pressure in 0.1 second using a device triggered by the R wave of the ECG with any desired delay. The ratio (R) of the area under the left radial time-concentration curve to that under the left femoral curve is a measure of the fraction of the injected dye which gets back to or beyond the origin of the left subclavian artery to be distributed on the next systole to both sampling sites in proportion to flow. R must be a function of the timing of the injection as well as the site of injection. It has been found that for injections made at the time of maximum back-flow velocity (first 0.1 second of diastole) $R = e^{-kx}$ for values of R between 1.0 and 0.1, where x is the distance (cm.) from the position where R equals 1.0 k, the fractional decay of R per cm. is greater than 1.0 (100 per cent decrease in ratio per cm. withdrawn) in normal subjects and less than 0.2 in patients with severe aortic insufficiency and in dogs with one leaflet of the aortic valve incised to the ring.

Circulation and Respiration in the Giraffe

James V. Warren, Durham, N. C., John L. Patterson, Jr., Richmond, Va., Joseph T. Doyle, Albany, N. Y., Otto H. Gauer, Bad Nauheim, Germany, E. N. Keen, Capetown, South Africa, Maurice McGregor, Johannesburg, South Africa, and Robert H. Goetz, Capetown, South Africa.

The giraffe represents an intriguing natural experiment in the adaptation of the circulation to gravitational stress. The respiratory problems created by the great tracheal length of the animal are hardly less interesting. In October 1956 an international team performed experiments on 4 animals in the Union of South Africa. All studied were confined in the vertical position and 1 also studied in the horizontal position after intravenous anesthesia.

Arterial blood pressure in the neck, corrected to heart level, ranged from 282/150 to 344/194 mm. Hg. In 1 bucking animal, pressure rose to 360/257 mm. Hg. Intracardiac pressures were measured with a Gauer miniature manometer. Mean right atrial pressure approximated atmospheric. Pulmonary arterial pressure was 75/25 mm. Hg. Cardiac output in 3 animals was 19.4, 41 and 49 L. per minute. Lowering the head of 1 animal to ground level produced little change in arterial pressure at heart level.

Respiratory minute volumes ranged from 75 to 175 L. per minute, tidal volumes from 2.7 to 4.1 L., oxygen consumption from 2.7 to 4.7 L. per minute. Mean respiratory rate was 40 per minute, higher than in the unconfined animal, and depth increased. Inspiratory pneumotachograms were plateau, almost rectangular, in shape. Arterial oxygen and CO_2 tensions were normal or slightly below normal by human standards, suggesting that in nonhyperventilating animals the pO_2 would be low. Inhalation of 10 per cent oxygen raised minute ventilation from 77 to 169 L. within 45 seconds. In 2 autopsied animals, tracheal volumes were 1.2 and 2.3 L. A pressure-volume diagram on excised lungs showed

the surprisingly small total lung volume of approximately 10 L.

It is concluded that the giraffe solves the problem of cerebral perfusion primarily by marked arterial "hypertension." It is likely that venous pressure at brain level is subatmospheric and aids cerebral perfusion. The inspiratory pneumotachogram is compatible with airway obstruction. Compensation for the large respiratory dead space apparently is effected either by large tidal and minute volumes, or by adaptation to reduction in arterial oxygen tension.

Resuscitation from Ventricular Fibrillation Following Acute Myocardial Infarction: Preliminary Report of an Experimental Study in Normothermic Dogs

Fred Wasserman, Herbert Keller, Guillermo Hamdan, Manuel Cardenas, Harry Crits, and Samuel Bellet, Philadelphia, Pa.*

The conversion of ventricular fibrillation occurring in association with acute myocardial infarction is an important problem both clinically and experimentally. Although many studies have been performed in converting ventricular fibrillation to normal sinus rhythm, there are few reports where this has been done with acute coronary occlusion.

The purpose of the report is to demonstrate the conversion of ventricular fibrillation to normal sinus rhythm utilizing readily available solutions in association with positive pressure respirations and cardiac massage. Twenty normothermic dogs with acute myocardial infarction and spontaneous or induced ventricular fibrillation were immediately given intracardiac potassium chloride in concentrations of 1.5, 3.0, 10, and 15 per cent. In all cases the ventricular fibrillation was converted to ventricular standstill. The time required for this bore a definite relationship to the concentration of potassium chloride used. Slow cardiac massage was instituted from the onset of the ventricular fibrillation until the animals developed cardiac standstill. Five milliliters of molar sodium lactate was then injected into both the right and the left ventricles. Cardiac massage was subsequently speeded and continued until effective mechanical contractions were able to sustain the heart spontaneously. When the continuous electrocardiogram showed the development of an electric focus, molar sodium lactate was administered intravenously at a rate of 5 ml. per minute. Seventy-five per cent of the animals in this study were restored to a supraventricular rhythm. In the remaining 25 per cent we could only restore the dogs to an idioventricular rhythm, without a palpable peripheral pulse.

The effects of isopropylnorepinephrine, Ringer's lactate (25 times concentrated), 0.9 M sodium bicarbonate and 10 per cent calcium gluconate on resuscitation from potassium-induced standstill were also observed.

Modifying Effects of Hyperpotassemia on Digoxin: An Experimental Study

Fred Wasserman, Guillermo Hamdan, Leonard Lecks, and Samuel Bellet, Philadelphia, Pa.*

The effect of hyperpotassemia on the tolerance to digitalis is of considerable clinical and experimental importance. The object of this study was to determine the alteration in tolerance to digitalis of dogs with varying degrees of hyperpotassemia. These effects of digitalis were studied in 21 nephrectomized animals.

The lethal amounts of digoxin utilizing identical normopotassemic animals were similar. In hyperpotassemic nephrectomized animals, the tolerance, as determined by the lethal dose, increases in curvilinear fashion between the serum potassium levels of 6 and 10 mEq. per L.; a maximum increase of 70 per cent more digoxin was necessary to kill the animals when the serum potassium reaches 10 mEq. per L.

The initial evidence of digitalis effect consisted of primarily RST-T changes and vagal arrhythmias. These changes were observed after 50 to 80 per cent of the lethal dose had been given. Extrasystoles occurred relatively infrequently as manifestations of digitalis intoxication in the presence of hyperpotassemia. In general, when clearly defined changes were present which could be attributed to digitalis they occurred relatively late and progressed rapidly to death. The changes resulting from the infusion of digitalis were easily differentiated with serum potassium levels between 6 and 10 mEq. per L. When the mean serum potassium concentration was greater than 10 mEq. per L., death either resulted from potassium intoxication alone or from a combination of potassium and digitalis. At such serum levels it was difficult to separate changes due to digitalis and those resulting from advanced potassium poisoning.

Short Term Functional Cardiac Transplants

Watts R. Webb, and Hector S. Howard, Jackson, Miss.

Transplantation of a cardiac homograft into its usual intrathoracic position capable of maintaining adequate cardiac function has not been previously reported. Though the immunologic responses of the host prevent long-term survivals at this time, the problems of technic and the time involved have offered a great challenge and, until now, prevented even short-term survivals.

With the demonstration that the heart, when perfused free of all blood elements and refrigerated in a nutrient medium, may remain viable and functional for at least 8 hours, adequate time has been gained for the technical procedure.

Numerous cardiopulmonary transplants have been performed quite successfully so far as immediate function is concerned. These lead to the physiologic impass of respiratory failure in the presence of total denervation of the lung.

Accordingly, technics have been developed for transplantation of the heart alone. This necessitates 8 vascular anastomoses. The veins are anastomosed by specially developed couples and the arteries by direct suture. The heart can be anastomosed into the recipient in approximately 30 to 40 minutes. The rather lengthy total time required to prepare the donor heart and the recipient dog necessitates refrigeration of the donor heart to maintain its viability during the period that it is without coronary blood flow. While careful timing of the operations on the donor and the recipient might allow a transplant to be done without refrigeration of the donor heart, the procedure has been developed so as to meet conditions of anticipated future clinical usage.

With these technics, it has been possible to achieve temporary survivals of the recipient dog, during which periods it is totally dependent on the functioning transplanted heart.

Influence of Acidosis on the Effectiveness of Vasopressor Agents

Max H. Weil, Duarte, Calif., Dudley B. Houle, E. B. Brown, Jr., Gilbert S. Campbell, Minneapolis, Minn. and Charles Heath, Edmonton, Alberta, Canada.

Clinical observations have indicated that patients with acidosis respond relatively poorly to sympathomimetic agents, and that responsiveness is improved by correction of fluid and electrolyte derangements. In order to study the effect of acidosis on cardiac and vascular responsiveness to sympathomimetic amines under controlled conditions, experiments were performed on dogs anesthetized with pentobarbital. Epinephrine, norepinephrine, and metaraminol were injected intravenously into animals which were maintained under conditions of respiratory acidosis produced by inhalation of 30 per cent CO_2–70 per cent O_2 gas mixture. This was contrasted to the response produced by the same dose when the dog was breathing room air or 100 per cent oxygen and the pH of the arterial blood was normal.

Mean arterial blood pressures and electrocardiograms were recorded, and pH determinations were made on arterial blood samples.

All of the agents were injected in quantities which produced ventricular extrasystoles with frequent runs of ventricular tachycardia at control pH values. However, these abnormalities of rhythm were minimal or absent when identical amounts of these agents were injected into acidotic animals.

Epinephrine, norepinephrine and metaraminol were also administered to dogs subjected to total cardiac bypass, using a pump homologous lung oxygenator. By this method, the effects of these drugs on the heart were excluded, and the pressor effect produced by action on the peripheral vascular bed was studied. Pressor responses under conditions of respiratory acidosis were uniformly much less in these animals than responses obtained in the same animals after the arterial blood pH was returned to or near normal values.

These findings suggest an explanation for the notably poor response to sympathomimetic agents observed during treatment of patients with coexisting shock and acidosis. They also offer an explanation for the rapid improvement in pressor response which followed elevation of the blood pH by intravenous infusion of molar lactate, in a number of patients with profound shock and coexisting acidosis.

Diagnostic Biopsy of the Pericardium and Myocardium

Milton Weinberg, Egbert H. Fell, and Joshua Lynfield, Chicago, Ill.

Surgical biopsy of the pericardium and myocardium is a procedure usually not considered as a diagnostic aid in patients with heart disease. There is a group of patients, however, in whom a diagnosis cannot be made by the conventional clinical and laboratory methods and in whom definitive treatment is often unnecessarily delayed or, more often, is based upon therapeutic trial. The case histories of such a group of patients are presented and the indications for surgical biopsy are discussed, particularly in regard to definitive treatment of these patients.

In 1 of these patients, under therapy for tuberculous pericarditis, the diagnostic biopsy proved to be a therapeutic procedure in itself. In 1 patient a specific diagnosis was established and proper therapy was instituted. In 4 other patients, although the diagnoses established by biopsy did not allow specific therapy, the exclusion of other possible diagnoses eliminated the previously desired regimens of trial medication.

Anniversary Reaction in Relation to Cardiovascular Disease

Edward Weiss, Philadelphia, Pa., Barney M. Dlin, Vancouver, B. C., H. Keith Fischer, and C. R. Bepler, Philadelphia, Pa.

Illness of emotional origin, including psychophysiologic reactions, often seem to occur on the anniversary of a significant event in the life of the patient. This is usually the death of some key figure with whom the patient has established a complex identification, and in whom hostility is usually noted. The patient is often completely unaware of the circumstances and only when his attention is called to the fact does he recall the anniversary or the tension

associated with it. This phenomenon is called the anniversary reaction. Closely related are illnesses which begin in connection with birthdays and holidays. For a variety of reasons, these situations apply especially to cardiovascular disease.

The anniversary reaction was found in 4 out of 43 cases of coronary occlusion studied from a psychosomatic viewpoint. Cases of cardiac neurosis, essential hypertension, and myocardial infarction will be cited to illustrate these relationships. It is not difficult to obtain this information if: (1) one is aware of the association and (2) of the importance of emotional factors in cardiovascular illness, which includes the ability to recognize the symptoms of depression, and (3) makes a habit of including important dates in taking the history.

The information is useful in helping patients to avoid trouble and also in helping them through difficult periods.

Effect of Myocardial Infarction on the Size of the Heart

Morris M. Weiss and Morris M. Weiss, Jr., Louisville, Ky.

A roentgenologic follow-up study was made of 489 patients surviving an acute myocardial infarction for at least 2 months, who had a normal-sized heart at the time of the infarction. Only those patients were included who had recovered from their presumed first infarction. The majority of the patients were observed from 1 to 10 years. Two per cent (8 cases) developed cardiac hypertrophy in the absence of generally accepted factors such as hypertension, valvular heart disease, or cor pulmonale. Cardiac enlargement was first noted from 6 months to 13 years after the onset of the infarction. All 8 patients who developed cardiac hypertrophy had associated congestive heart failure. Multiple myocardial infarctions did not cause cardiac hypertrophy in the absence of congestive failure. Our opinion is that cardiac hypertrophy develops with congestive failure which, in turn, results from a myocardial aneurysm and/or extensive myocardial fibrosis, complications of the myocardial infarction.

Comparative Cardiac Effects of Various Sympathomimetic Amines

James W. West, Santiago V. Guzman, and Samuel Bellet, Philadelphia, Pa.*

The direct cardiac effects, following intracoronary arterial injections of isoproterenol (0.002 to 0.06 μg. per Kg.), levarterenol (0.01 to 0.05 μg. per Kg.), epinephrine (0.015 to 0.05 μg. per Kg.), epinine (0.25 to 0.5 μg. per Kg.), metaraminol (0.25 to 0.5 μg. per Kg.), mephentermine (0.75 to 5.0 μg. per Kg.), phenylephrine (2.5 to 10.0 μg. per Kg.), and methoxamine (1 to 400 μg. per Kg.), on coronary blood flow, myocardial contractility and rhythmicity were studied in dogs anesthetized with pentobarbital sodium or morphine-chloralose. Catheterization of the right coronary, circumflex and anterior descending branch of the left coronary artery via a carotid artery and cannulation of the coronary sinus via a jugular vein were accomplished under fluoroscopic guidance. Coronary blood flow was measured directly by collecting blood for a measured time from the coronary sinus cannula. Continuous electrocontractility was determined by means of a Walton strain gage. The chest remained intact in all preparations except those involving measurements of myocardial contractility.

The observed effects varied according to the coronary branch into which the drugs were injected. In the left anterior descending branch the main effects were on myocardial contractility and coronary blood flow, both of which were increased by all the agents except methoxamine. This either did not affect coronary blood flow or it produced a slight decrease (12 per cent). Myocardial contractility was not noticeably affected by doses of methoxamine up to 0.01 mg. per Kg.; it was depressed by doses greater than this. Right coronary and left circumflex injections, in addition to their effects on myocardial contractility and coronary blood flow, increased heart rate. Right coronary injections of these sympathomimetic amines, except methoxamine, produced a sinus tachycardia as a result of directly stimulating the S-A node, while left circumflex injections of these same agents with the exception of methoxamine directly stimulated the A-V node, producing a nodal tachycardia. Methoxamine, when injected in either vessel, produced no change in heart rate.

In the order of their effectiveness (isoproterenol, levarterenol, epinephrine, epinine, metaraminol, mephentermine, phenylephrine), all of these sympathomimetic amines increased coronary blood flow, myocardial contractility and heart rate. Methoxamine lacks all of these effects.

Severe Arteriosclerosis Produced in the ACTH-Treated Rat

Bernard C. Wexler and Benjamin F. Miller, Cincinnati, Ohio.

It has been observed that clinical endocrine imbalance, e.g., Cushing's disease, or experimentally-produced endocrine imbalance, e.g., chronic administration of desoxycorticosterone, leads to accelerated vascular disease. We have attempted to mimic this situation experimentally by chronic administration of ACTH.

Male and female Sprague-Dawley rats were unilaterally nephrectomized to increase their sensitivity to circulating steroids. After 10 days postoperative rest, they were given subcutaneous injections of ACTH on alternate days for 7 weeks.

At autopsy, a striking sex dichotomy was en-

countered. The female rats showed gross arteriosclerotic lesions accompanied by ectasia of the aorta, similar to the senile human. In the very severe cases, outpouchings occurred in the descending aorta. These outpouchings were confirmed to be true aneurysms on histologic examination. The arteriosclerotic lesions followed a distribution pattern similar to that seen in the human. Where sclerosis was advanced, the entire aortic tree was involved, with placodes extending into the more peripheral vessels. The male animals developed periarteritis nodosa. In no instance was arteriosclerosis observed in males.

The pathologic changes could be produced whether the kidney was removed or not. In general, the incidence and severity of sclerosis was accentuated in those animals subjected to the additional stress of nephrectomy in conjunction with exogenously administered ACTH. Further, the degree of thymic involution brought about by glucocorticoid excesses proved to be a reliable index of the severity of the arteriosclerotic process. Serum cholesterol levels do not seem to correlate with the severity of the vascular lesions.

These studies indicate that greater emphasis should be placed on the role of stress and endocrine activity, especially the pituitary-adrenal system, in the pathogenesis of arteriosclerosis. It is noteworthy that our technic produces severe lesions consistently in the rat, an animal hitherto extremely resistant to experimental arteriosclerosis.

Clinical Usefulness of Vectorcardiography: Importance of the Method of Data Analysis

Gerald H. Whipple and Harold D. Levine, Boston, Mass.

Vectorcardiography gives a more obvious depiction of phase relationships inherent in its conventional electrocardiographic components but is of minor help in determining more precisely the orientation of a cardiogram in electrical space. A valid appraisal of the clinical role of vectorcardiography should be based primarily on determination of the diagnostic significance of variations in phase relationships. Most studies, however, have emphasized spatial orientation. Because various cardiographic patterns are observed in a given clinical condition, the usual practice of using clinical or anatomic groupings rather than vectorcardiographic patterns as the starting point for analysis also interferes with a satisfactory evaluation of the technic.

In the present study, 1,500 consecutive adult spatial vectorcardiograms were studied with primary emphasis on variation in QRS phase relationships. Quantitative vectorcardiographic criteria were established to subdivide large groups of cases whose electrocardiograms were similar when analyzed by conventional methods. Within a group showing a given vectorcardiographic pattern, there was often a consistent trend in associated clinical and anatomic data. Clinically useful patterns were found most often in association with combined ventricular hypertrophy which would not have been apparent if conventional electrocardiographic analysis alone had been used. The clinical data in all cases conforming to one of these patterns will be used for illustration. Thirteen of the 16 cases in this group had lesions which are associated with combined ventricular hypertrophy confirmed at cardiac surgery, cardiac catheterization, or autopsy. In the remaining 3 cases, combined ventricular hypertrophy was probable on clinical grounds. As indicated, the pattern was never seen in normals, although the electrocardiographic QRS complex was normal in 9 of the 16 cases.

The analytic method described, based primarily on phase patterns, selectively sorts out the occasional case in which vectorcardiography has been found to be of distinct supplemental value clinically.

Significance of Upright QRS Complexes in Lead V_{4R}

Gerald H. Whipple and Jay D. Coffman, Boston, Mass.

Some patients with right ventricular hypertrophy may show obvious electrocardiographic evidence of it only in special leads from the right chest. However, when lead V_{4R} was taken routinely, complexes which would be interpreted as indicating right ventricular hypertrophy by existing criteria were found in a small number of normal individuals. To evaluate these observations, leads were taken from the fourth and sixth intercostal spaces as well as in the fifth intercostal space (V_{4R}) in the right midclavicular line in 540 consecutive adult patients.

QRS complexes of Rs or monophasic upward R configuration in V_{4R} were found in 7 patients with no clinical evidence of cardiovascular or pulmonary disease, most often in females with electrically vertical hearts. Two other clinically normal patients showed rsR′ configurations in this lead with QRS complexes of normal duration. Complexes of the various types referred to were found in normals 1 interspace below V_{4R} in 15 instances but were found 1 interspace higher than V_{4R} in only 3 cases. The same decreasing incidence of dominant R waves as the electrode was moved cephalad was found in patients with probable right ventricular hypertrophy.

It is concluded that one cannot separate the QRS complexes of normals from those with right ventricular hypertrophy in an absolute fashion by the use of V_{4R}; a distinct overlap exists. Particularly when the placement of V_{4R} is a little low, but also correct, one selectively picks up a number of cases with probable right ventricular hypertrophy as well as a few normals. Normals appear to be almost totally excluded by placing the lead 1 interspace

higher than V_{4R}, but such a lead is also considerably less sensitive to actual right ventricular hypertrophy.

Left Heart Angiography in the Diagnosis of Mitral or Aortic Insufficiency

Robert J. Wilder, Baltimore, Md., and Howard L. Moscovitz, New York, N. Y.

The detection of significant incompetence of the aortic or mitral valve, particularly when these lesions are combined with valve stenosis, continues to present a problem in the preoperative selection of candidates for valvulotomy. Roentgen contrast visualization of the regurgitant jet is incontestible evidence of valve incompetence, in the absence of arrhythmia.

Experimental mitral or aortic insufficiency was produced in a group of 38 dogs by avulsion of a segment of a valve leaflet. A no. 8 Lehman aortographic catheter was passed in retrograde fashion through a femoral artery and positioned in the left ventricle or just above the aortic valve. Urokon, 1 ml. per Kg. of 70 per cent solution, was rapidly injected, and a single spot roentgenogram taken near the end of the injection.

The normal aortic or mitral valve prevents regurgitation of radiopaque material during regular sinus rhythm. When these valves are rendered insufficient, there is no difficulty in detecting left atrial reflux in mitral insufficiency or left ventricular regurgitation in aortic insufficiency. Quantitation of the degree of incompetence is, however, more difficult than the mere demonstration of its presence, but small jets could be easily differentiated from massive ones.

When mitral stenosis was combined with mitral insufficiency, the degree of mitral reflux was reduced but was not significantly eliminated until a high left atrioventricular filling pressure gradient appeared. The stenotic area could be clearly visualized on the roentgenograms.

High-speed motion pictures were taken of the intensified image of a fluoroscopic screen, at the rate of 48 frames per second, during intracardiac injection of radiopaque substance. While the details of blood flow and valve leaflet motion were depicted in far greater detail, this method did not appear to be superior to the spot-film technic in detecting significant degrees of regurgitation.

Simple Exercise Test for the Evaluation of Cardiac Function

M. Henry Williams, Jr., Lenore R. Zohman, Valhalla, N. Y., and Herbert S. Heineman, Durham, N. C.

An exercise test has been developed for the study of cardiac function during standardized exercise. The supine subject pedals a bicycle-type exerciser against a standard resistance (equivalent to 7 lbs.) at various rates of speed established by a metronome. During the last 2 minutes of a 5-minute exercise period, electrocardiogram and respiratory rate are recorded while expired air is collected for measurement of oxygen consumption and minute ventilation. There is a linear increase in oxygen consumption, with increased rates of pedaling equivalent to 8 cc. of oxygen consumption per pedal. This relationship is independent of age, size, or sex of the subject. There is also a linear increase in pulse rate with increased oxygen consumption, normal males developing less increase in pulse rate (6 heart beats per minute per 100 cc. of oxygen consumption) than normal females (9 beats per minute per 100 cc. of oxygen consumption). Elderly subjects develop similar degrees of tachycardia to young subjects. There is no correlation between the pulse increase/increased oxygen consumption and body surface area. Since pulse increase is linear with respect to the oxygen consumption, and the latter is linear with respect to pedals, it is possible, though less precise, to simplify the test by calculating the increase of pulse rates/pedals. In normal males the pulse increases 5 beats per minute per 10 pedals, and in females 7 beats per minute per 10 pedals.

Patients with cardiac failure generally have an increased ratio of pulse rate increase/oxygen consumption increase, whereas this ratio is normal in patients with cardiac or pulmonary disease who do not have congestive heart failure. In addition, in patients with heart disease, a subnormal increase of cardiac output during exercise is paralleled by an abnormal increase of heart rate. The latter approaches normal after commissurotomy for mitral stenosis or after digitalization of patients in congestive failure.

Dietary Protein, Fat and Choline in the Production of Cardiac and Hepatic Lesions in Mice

William L. Williams, Minneapolis, Minn.

Young adult mice with an initial body weight of 22 to 24 Gm. were fed one of the following diets:

Diet I (300 mice): 7 per cent protein (as yeast, soya flour or casein), 12.5 per cent fat, 75 per cent carbohydrate, 4 per cent salt mixture (℔2, U.S.P. XIII) and 1.5 per cent vitamin supplement. Myocardial necrosis and fibrosis with deposition of ceroid and calcium were observed in 70 per cent of the mice within 30 to 283 days (average 97). The incidence of nonlipotic hepatic necrosis was 8 per cent within 60 to 272 days (average 153). The incidence of myocardial damage was increased by l-cystine (0.5 Gm. per 100 Gm. diet) and decreased by α-tocopherol (2.5 mg. weekly).

Diet II (choline deficient, 200 mice): 8 per cent casein, 38.5 per cent fat, 47.5 per cent carbohydrate, 0.5 per cent l-cystine, and salts and vitamins as above. Hepatic parenchymal liposis was progressive for 30 days and was followed by formation of fatty cysts, deposition of ceroid, nodular parenchymal

hyperplasia and reticulinosis. Myocardial lesions were limited to focal necrosis and fibrosis in 16 per cent (8 of 50) of these mice after 2 to 10 months (average 168 days) of restriction to the choline-deficient diet.

Diet III (77 mice): diet II plus a supplement (0.5 Gm. per 100 Gm. of diet) of choline sufficient to prevent hepatic liposis. Myocardial necrosis and fibrosis were observed in 61 per cent (22 of 36) of these mice within 2 to 10 months (average 161 days).

Combined deposits of ceroid and calcium were characteristic of the myocardial lesions of mice fed the low protein-low fat diet (I), but the livers were free of ceroid. When the low protein-high fat diets (II and III) were fed, the myocardial lesions contained no ceroid. Liposis was massive, and ceroid was abundant in livers of mice fed the choline-deficient diet (II).

Electrocardiograms of 90 Patients with Acrosclerosis and Progressive Diffuse Sclerosis (Scleroderma)

John H. Windesheim and Thomas W. Parkin, Rochester, Minn.

The records of all patients with scleroderma seen at the Mayo Clinic during the years 1949 through 1953 were reviewed. There were 90 who had electrocardiograms available for study. The diagnosis in 63 patients was acrosclerosis, 27 were diagnosed as having progressive diffuse sclerosis.

The youngest patient was 9 years of age, the oldest 87 years, mean age was 46 years. There were 29 males and 61 females. Only 5 of the patients with acrosclerosis had abnormal electrocardiograms: 2 showed evidence of an old anterior wall scar, 1 left ventricular hypertrophy, 1 atrial fibrillation, and 1 a minor intraventricular conduction defect with T wave change. Three of the patients with diffuse progressive sclerosis had abnormal electrocardiograms: 2 showed low amplitude QRS complexes with gross T wave abnormalities, and 1 a right bundle-branch block pattern.

Only 2 patients had evidence of congestive heart failure, both had severe diffuse progressive sclerosis. The electrocardiograms of both of these patients showed low amplitude QRS complexes with gross T wave abnormalities.

Studies of Pure Veratrum Alkaloids, Protoveratrine A, Protoveratrine B, and Germitetrine B

Bertram M. Winer, Boston, Mass.

Our previous preliminary studies demonstrated quantitative and qualitative differences in action between protoveratrine A and protoveratrine B after oral and intravenous administration in man. The present report confirms and extends these observations and presents studies of a third tetraester veratrum alkaloid, germitetrine B. Protoveratrine A and protoveratrine B differ in ester structure by a single hydroxyl group but have the same alkamine. Germitetrine B has the empirical ester structure of protoveratrine B but a different alkamine.

Protoveratrine A and protoveratrine B were administered separately by the intravenous route at varying dosage levels to each of 14 patients, and germitetrine B to 8 of these patients. Each alkaloid had strong hypotensive activity after small doses, germitetrine B > protoveratrine A > protoveratrine B. However, protoveratrine B had a wider range between hypotensive and emetic activity than the other alkaloids ($p < .001$).

Orally, both protoveratrine A and germitetrine B had hypotensive activity in doses roughly 4 times the intravenous dose. Both had a narrow range between hypotensive and emetic activity.

Protoveratrine B was administered orally to 23 patients. There were 4 striking differences when compared to the other alkaloids: 1. The hypotensive effect was longer in duration. 2. An emetic effect was rare. 3. Neuromuscular symptoms were common, although mild. 4. Doses of more than 20 times the intravenous dose were required for hypotensive activity. Of considerable interest, acetylsalicylic acid and sodium salicylate were found to increase the hypotensive response, but not sodium acetate.

These findings indicate that there are clinically significant differences in the activities of pure tetraester alkaloids of veratrum. Because of a wider range between therapeutic and emetic doses, protoveratrine B is the veratrum alkaloid of choice for intravenous use. Orally this alkaloid also offers advantages over other veratrum alkaloids, but its use is limited by neuromuscular effects and some variability in response. The observed differences between these alkaloids appear dependent, not only on the specific ester groups, but upon their spatial configurations.

Diagnosis of Early Myocardial Infarction by Direct Body, Head-Foot Ballistocardiography

Nahum J. Winer, New York, N. Y.

The electrocardiogram often fails to detect early myocardial infarction. To date, ballistocardiography has failed to indicate any one component whose alteration is characteristic of infarction. Theoretically, HI, especially in acceleration, should receive most attention since it represents the beginning of systole. The "Arbeit d-v-a" circuit with direct body pickup records acceleration in greater frequency than other methods, representing the second derivative of acceleration of the ultra-low frequency bed and affords a proposed differential in HI configuration of shallow, irregular character reflecting the impaired dynamics of infarction. Need for higher frequency is indicated by a case of pectus excavatum during suspended midinspiration following smoking. While displacement showed progressive, organically sug-

gestive, deterioration of HI, acceleration showed its progressive improvement indicating its functional nature believed due to rapid exhaustion of the pulmonic pool.

Recording in suspended midinspiration is emphasized to exclude functional deterioration of relaxed breathing attributed to splanchnic pooling and comparable corrected by abdominal support. Organic deterioration persists.

Nine cases are presented: 6 organic and 3 functional.

Organic: Four had precordial pains; 2, none. All showed HI deterioration. In the 2 without pain, while ECG was unaltered, infarction was supported by other laboratory evidence, including serum transaminase. In 2 others with essentially unaltered ECG, death occurred suddenly within 3 months of examination.

Functional: Three cases; all with pains. One post-myocardial infarction showed alternating normal and abnormal resting BCG, the first deteriorating following exercise. Both were corrected by suspended midinspiration. A second presented ECG alterations suggesting myocardial pathology. BCG was normal. A third suspected case had a normal BCG. All were encouraged into activity.

Conclusion: The portable head-foot direct body BCG may detect early myocardial infarction in the presence of unaltered ECGs, by HI deterioration observed particularly in higher frequencies of acceleration which persists during suspended midinspiration.

Effect of Exercise and Androgen in Cholesterol-Fed Pullets

Harry Y. C. Wong, Frank B. Johnson, and Abbie K. Wong, Washington, D. C.

The present investigation was undertaken to study the effects of exercise and testosterone propionate on the blood cholesterol, aortic and coronary atherosclerosis of pullets fed a high cholesterol diet. After 9 weeks on an "atherogenic" diet, consisting of 2 per cent cholesterol and 5 per cent cottonseed oil, the following results were observed: (1) cholesterol-fed pullets not exercised had the highest incidence of aortic atherosclerosis and blood cholesterol; (2) birds on a cholesterol diet and exercised had a lower incidence than the preceding group; and (3) pullets on a cholesterol diet treated with testosterone propionate, and similarly treated birds which were exercised, had a lower blood cholesterol and aortic atherosclerosis. All pullets, which were exercised, were rotated in a treadmill twice daily for 30 minutes, 5 days weekly at 6 r.p.m. We conclude from our data that exercise did not significantly reduce the blood cholesterol when compared to the cholesterol-fed group only. This is contrary to previous reports from our laboratory that exercise resulted in a marked reduction of the blood cholesterol, with a subsequent reduction in aortic and coronary atherosclerosis of young cockerels on a similar diet. However, birds treated with testosterone propionate, or similarly treated pullets, had a significantly lower blood cholesterol and severity of aortic atherosclerosis when compared to the cholesterol-fed only. A discussion will be presented regarding the differences in results of blood cholesterol of the 2 sexes, as well as the influence of exercise and testosterone propionate on the coronary arteries.

Comparison of Oral Penicillin and Oral Sulfadiazine in a Controlled Study of Three Methods of Prophylaxis Against Streptococcal Infection in a Population of Rheumatic Children

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It has been generally assumed that orally administered penicillin is inherently superior to sulfadiazine as a prophylactic agent against streptococcal infections and recurrences of rheumatic fever in known rheumatic subjects. This unproved hypothesis is probably based on the fact that penicillin is bactericidal, whereas the sulfonamides are bacteriostatic. The validity of this assumption has not previously been subjected to rigorous testing in a controlled study involving groups which are comparable as to age, race, number of attacks of acute rheumatic fever, and duration of time since the last known attack.

On April 30, 1957, Irvington House finished the third year of a carefully controlled 5-year statistical study of 400 rheumatic children maintained on 3 different prophylactic agents. The 3 regimens under study are: (1) sulfadiazine, 1.0 Gm. per day by mouth in a single dose, (2) penicillin, 200,000 units a day by mouth in a single dose, one-half hour before breakfast, and (3) benzathine penicillin G, 1.2 million units in 2 ml. bimonthly intramuscular injection.

Streptococcal infections were detected as follows: Throat cultures were taken on every patient at each monthly clinic visit, and all B-hemolytic streptococci were grouped with an antiserum to the group A streptococcus. Antistreptolysin O determinations were done on each bleeding from every patient. These bleedings were taken bimonthly and whenever an elevation was found in the routine antistreptolysin O, a serial determination of antistreptolysin O, of antistreptokinase, and of antihyaluronidase was carried out on several successive monthly bleedings from the patient.

Recurrences of acute rheumatic fever were diagnosed with the aid of the modified Jones criteria.

The number of streptococcal infections detected

in each of the prophylaxis groups during the 3-year period was: benzathine penicillin G, 21; sulfadiazine, 67; penicillin, 57. The number of infections followed by recurrences of acute rheumatic fever and the percentage of the total infections for each group which this number represents were as follows: benzathine penicillin G, 1 (5 per cent); sulfadiazine, 6 (9 per cent); oral penicillin, 12 (21 per cent).

These data do not support the assumption that oral penicillin prophylaxis at the dosage used is more effective than oral sulfadiazine in preventing recurrences of rheumatic fever. More definitive conclusions will depend on the accumulation of additional data in the next 2 years of the study and observations regarding persistence of the present pattern of recurrences in the prophylaxis groups.

Self-Adjusting Counter Pressure Hydrostatic Stocking: Its Use in the Treatment of Venous Stasis Ulcers

J. Edwin Wood, Boston, Mass.

A stocking was constructed so that it exerted pressure upon the leg equivalent to the vertical hydrostatic distance from any point on the leg to the right atrium, regardless of the position of the patient. This stocking was used for the treatment of ambulatory patients with chronic venous stasis ulcers.

The Nylon-cotton stocking, which could be fitted to the individual patient, contained a neoprene bladder covering the medial surface of the calf and ankle. A rubber tube connected this bladder to another smaller closed collapsible bladder suspended in the axilla. The entire system was filled with 750 ml. of water. Thus, the patient's leg was constantly exposed to the pressure of an external column of water reaching to the level of the right atrium (axilla).

Pressures were measured directly at 12 points beneath the stocking, in the recumbent, sitting, and standing positions on 5 subjects. Pressures varied no more than 6 ml. of water from the pressure predicted from the vertical distance between the point of measurement and the level of the axillary bladder.

Four patients with venous stasis ulcers were treated with the stocking while continuing their usual occupations. Excepting biweekly changes of dressings, no other therapy was given. Healing of ulcers, which were at least 2.5 cm. in diameter, occurred within 3 to 5 weeks. Another patient who had had repeated ulcerations of the leg despite varied medical and surgical therapies wore the stocking for 12 months with prompt healing of 2 ulcers and no recurrence during this time. He stopped wearing the stocking and an ulcer reappeared. He resumed use of the stocking and the ulcer promptly healed.

The selfadjusting counter pressure principal is a useful practical method for treating ambulatory patients with chronic venous stasis ulcers.

Plasma Concentrations of Epinephrine and Arterenol During Cardiopulmonary Bypass

Eugene F. Woods, James A. Richardson, William H. Lee, Jr., John D. Ashmore, and Edward F. Parker, Charleston, S. C.

In the course of experimental direct vision intracardiac surgery in this laboratory, hemodynamic changes indicative of increased sympathoadrenal activity have been noted frequently. In the present study, plasma concentrations of epinephrine and arterenol were determined in dogs and patients during cardiopulmonary bypass. Wherever possible, variations in myocardial contractility and arterial blood pressures were correlated with measured changes in plasma amines. In all experiments, cardiac bypass was accomplished with a DeWall type bubble oxygenator (Brunswick model) and Sigmamotor pump apparatus. The fluorimetric method of Weil-Malherbe and Bone as modified by Richardson et al., was used for the assay of epinephrine and arterenol. For the measurement of cardiac contractility, a strain gage arch was sutured directly to the surface of the right ventricle. Validity of these measurements and their relationship to other cardiovascular events have been reported. The results of the present study show that, during cardiac bypass in dogs, reduction of perfusion flow rates to levels at which heart force and blood pressure were significantly lowered had the effect of producing marked increments in plasma concentrations of epinephrine and arterenol. The larger increase consistently occurred in the epinephrine concentration with a lesser grade of change occurring in the arterenol concentration. In experiments with higher flow rates, cardiac contractility and plasma adrenergic amines showed no substantial variations from control values. Similar results have been obtained in preliminary studies on patients undergoing corrective cardiac surgery. In the course of this study it was also noted that simply circulating fresh whole blood from donor dogs through the bypass pump apparatus substantially increased the plasma concentrations of epinephrine and arterenol. Evidently agitation is not the sole explanation since these changes in catechol amine levels were not obtained when blood was vigorously shaken in a mechanical mixer.

Simple Method Using Indicator-Dilution Curves to Differentiate Patients with Predominant Mitral Stenosis from those with Predominant Regurgitation

Edward Woodward, Jr., Howard B. Burchell, and Earl H. Wood, Rochester, Minn.

Specific alterations in dilution curves produced by valvular regurgitation were investigated. Dilution curves recorded by oximetry at the radial artery and the ear following injection of T-1824 into the

pulmonary artery in 11 healthy subjects and 30 patients with mitral valve disease were studied. Alterations in components of the curves produced by nonspecific changes in cardiac output and central blood volume which commonly occur from patient to patient and are exaggerated by congestive heart disease can, as demonstrated by Broadbent, be compensated for to a high degree by calculating ratios of individual time or concentration components. The disappearance-slope ratios and variance ratios of Korner and Shillingford were also calculated for these curves. Each ratio studied was related to the degree of mitral insufficiency based on a combination of surgical, clinical and catheterization findings. The minimal concentration (C_L) (measured between the peak and systemic recirculation waves) divided by the systemic recirculation concentration (C_R) was the only ratio which gave complete separation of patients with predominant stenosis from those with predominant mitral regurgitation. All patients with pure or predominant stenosis showed a recirculation peak, while this peak was not detected in 7 of 15 patients with predominant regurgitation. In those cases the value for C_L/C_R was designated as greater than one. The mean value for the C_L/C_R ratio for patients with predominant stenosis (0.35; range 0.16–0.52) was approximately one-half the value for patients with predominant regurgitation (0.76; range 0.73–>1.0). In addition to providing the best differentiation the C_L/C_R ratio has considerable practical value, since C_L and C_R can be measured directly from continuously recorded curves and the ratio calculated without the necessity of converting deflections to dye concentration, corrections for dye dose, or laborious mathematical manipulations as required for the Korner-Shillingford ratios.

Demonstration and Localization of Left-to-Right Shunts and Valvular Regurgitation by Indicator-Dilution Technics

J. Leo Wright, H. J. C. Swan, and Earl H. Wood, Rochester, Minn.

Indicator-dilution curves characterized by a relatively small peak concentration, disproportionate prolongation of the disappearance slope and an ill-defined or absent systemic recirculation peak may indicate the presence of either an arteriovenous shunt or valvular regurgitation.

Localization of these defects can be accomplished during catheterization of the right heart, left heart, or aorta by studying the similarity or dissimilarity in contour of dilution curves obtained by use of: (1) multiple appropriately selected injection sites, (2) multiple appropriately selected sampling sites, or (3) combinations of these 2 technics.

Localization of an arteriovenous shunt from dilution curves recorded at a single peripheral sampling site requires a normal contour following injection of the indicator into the left heart or systemic circulation downstream to the site of the defect, and an abnormal curve following injection upstream to the defect. Likewise, identification of an incompetent valve requires a normal contour at the periphery following injection just distal to the next competent valve downstream to the incompetent valve and an abnormal curve following injection at an upstream site or immediately distal to an incompetent valve.

Use of multiple sampling sites makes possible localization of defects with a single injection of indicator into the venous circulation since an essentially normal curve may be recorded from sites in the right heart upstream to a left-to-right shunt or from the right or left heart upstream to a competent valve, and simultaneously an abnormal curve will be recorded from sites at or downstream to the defect or incompetent valve.

These technics are of greatest practical diagnostic value for detection and localization of abnormalities not easily identified with certainty by ordinary catheterization procedures, such as, demonstration of multiple defects with coexisting left-to-right shunts, localization of incompetent valves, and differentiation of various types of aortic-pulmonary communications.

Effects of Intravenous Hexamethonium on Pulmonary Circulation in Mitral Stenosis

Paul N. Yu, Rochester, N. Y., Robert E. Nye, Hanover, N. H., Frank W. Lovejoy, Bernard F. Schreiner, and Bernard J. B. Yim, Rochester, N. Y.

Hexamethonium bromide was administered intravenously to 27 patients with mitral stenosis in doses sufficient to lower the brachial artery systolic pressure by at least 30 mm. Hg. In the majority of observations, there were significant decreases in total pulmonary resistance, pulmonary artery pressures (PA_m), and pulmonary arterial wedge pressures (PCP). The decreases in pulmonary artery pressures were roughly proportional to the changes in brachial artery pressures but were not related to changes in cardiac index or in PA_m-PCP gradient, both varying at random.

These observations imply that hexamethonium in some way reduced left atrial pressure without reducing flow, thus permitting a parallel reduction in pulmonary artery pressure. It was probably not due to passive shifts of blood from lung to periphery or of vasodilatation of the pulmonary arterioles or venules. The greatest reduction in PCP per unit flow were obtained in those patients with the most marked decreases in heart rate. However, some patients obtained significant decreases in PCP related to flow without change in heart rate. Part of the explanation may lie in decrease in left ventricular diastolic pressure as observed in normal dogs by Wakim. Only 6 of our patients had elevated left ventricular diastolic pressure during subsequent thoracotomy.

Another possible explanation is vasodilatation in the extensive anastomatic connections from pulmonary vein to azygos vein via the bronchial vein which exists in mitral stenosis. Any diversion of blood through this system may reduce the mitral valve flow and left atrial pressure, but would not be detected by the application of the direct Fick principle.

Hexamethonium was used successfully in the treatment of acute pulmonary edema which developed in 5 patients with mitral stenosis.

Spatial Vector Electrocardiography: Method and Average Normal Vector of P, QRS, and T in Space

Zang Z. Zao, George R. Herrmann, and Milton R. Hejtmancik, Galveston, Tex.

A model for spatial vector electrocardiography from 12 routine leads is presented. It consists mainly of a vertical circular form representing 6 limb lead "polarity" circles in concentric arrangement, a horizontal circular form representing 6 precordial lead "polarity" circles in concentric arrangement, and a center vector origin. This model correlates visually polarities written in the 12 routine leads and corresponding spatial heart-vector at a glance.

The distribution of vectors of P, QRS, and T in the RLF plane and "horizontal" plane were thereby obtained from corresponding area polarities in 1,000 normal electrocardiograms, under the criteria of Frank N. Wilson. The average normal vectors of P, QRS, and T in space are presented.

The model has proved to be very useful in clinical teaching for the visualization of any heart-vector in space. It should be noted that the present model may be adapted easily to a method of more accurate spatial vector electrocardiography of 12 leads based on Burger lead vector concept (similar in principle in the functional orthogonalization of vectorcardiographic systems) with the patient electrodes in the routine positions. We are advancing this method.

Einthoven Assumption in Circular Forms: Study of 10,000 Electrocardiograms

Zang Z. Zao, George R. Herrmann, and Milton R. Hejtmancik, Galveston, Tex.

Present circular form is the geometric consequence of the Einthoven assumption. It consists of 6 "polarity" circles in concentric arrangement, representing, from within outwards, limb leads 1, 2, 3, R, L, and F. Each "polarity" circle is composed of a positive semicircle, a negative semicircle, and 2 zero potential boundaries. The relation between the "polarity" circle and axis of a same lead is such that a line joining the 2 zero potential boundaries of the former would be perpendicular to the axis. This form correlates visually inscribed polarities in 6 limb leads and corresponding RLF plane heart-vector at a glance.

This report presents the heart-vector data thereby obtained by the application of this system to the analysis of area polarities in electrocardiograms of normal, right ventricular hypertrophy, left ventricular hypertrophy, right bundle-branch block, and left bundle-branch block, classified under the criteria of Frank N. Wilson. Several vector electrocardiographic criteria are given.

This circular form was found to be very useful in clinical routine.

Use of Venous Angiocardiography in the Diagnosis of Acute Dissecting Hematoma of the Aorta

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Although a dissecting hematoma of the aortic wall may be suspected by clinical and conventional roentgenographic studies, the advent of surgery for its relief demands precise diagnosis. Such precision is possible by venous angiocardiography, a fact which has not been generally appreciated. Moreover, venous angiocardiography has not been used in the presence of an acute dissecting hematoma because of fear of reactions. The purpose of this paper is to show that venous angiocardiography is a safe procedure which can establish the diagnosis beyond question immediately after the onset of symptoms of an acute dissecting hematoma of the aortic wall. We have performed over 300 venous angiocardiographic studies in adults with a variety of serious pulmonary and cardiac disorders, including cardiac failure. Many of our studies have been done in outpatients. We have had no deaths. Morbidity is limited to a rare transient urticaria and an infrequent trivial thrombophlebitis at the site of injection. It was because of this favorable experience that we employed venous angiocardiography as a diagnostic precedure in patients clinically suspected to have acute dissecting hematoma. No untoward reactions occurred, and the studies were diagnostic. The diagnostic angiocardiographic pattern consists of visualizing 2 aortic lumens, the true one and the false one. The densely opacified main aortic channel gives rise at the site of dissection to 2 lumens separated by a thin radiolucent layer. The true lumen has smooth borders and is as densely opacified but usually narrower than the main aortic channel. The false lumen is represented by a crescentic mass of soft tissue density which surrounds the true lumen. Additional changes produced by aneurysms of the outer or inner walls are readily recognized. Cases of acute and chronic dissecting hematoma illustrating these changes will be demonstrated. It is concluded that venous angiocardiography is a safe and diagnostic procedure in the presence of acute dissecting hematoma of the aortic wall.

Hemodynamic Effects of Vasodilatation Induced by Sodium Nitrite in Congestive Heart Failure: Relationship to Starling's Law of the Heart

Albert M. Ziffer, Bertha Rader, and Ludwig W. Eichna, New York, N. Y.

This study proposed to determine whether Starling's law of the heart applies to man. In previous observations, lowering ventricular filling pressure by the ganglionic blocking agent Arfonad resulted in decreased cardiac output in control subjects and increased cardiac output in patients with congestive heart failure. However, due to a concomitant fall in arterial pressure, cardiac work remained unaltered in congestive heart failure and fell in normal subjects. Starling's law appeared to hold in normal circulation but not in congestive heart failure. Unfortunately, the fall in arterial pressure introduced conditions under which the Starling effect may not apply. Accordingly, the problem was reinvestigated using sodium nitrite, since its predominantly postarteriolar site of action suggested that filling pressure might be lowered without lowering arterial pressure.

Ten studies, utilizing cardiac catheterization, were performed on 7 patients; 3 with normal circulation, 5 with congestive heart failure, and 2 compensated with digitalis. After 3 control determinations, 0.2 Gm. sodium nitrite was given orally, and determinations were repeated after 15, 30, 60, and 90 minutes. Filling pressure was decreased maximally between the thirtieth and forty-fifth minute. Right ventricular end-diastolic or atrial pressure fell an average 3 mm. Hg in control subjects, and 6 mm. Hg in congestive heart failure. Mean systemic arterial pressure decreased at most 5 to 10 mm. Hg. As filling pressure fell, cardiac output decreased in 2 control subjects by 0.6 L. per minute, and rose slightly in the third, an unstable subject; cardiac output increased, by 0.34 to 0.73 L. per minute, in all subjects with congestive heart failure. In 2 compensated cardiac subjects, cardiac output rose only one-half as much. The A-V oxygen difference increased in control subjects and fell in congestive heart failure.

Since arterial pressure was essentially maintained, it can be assumed that with decreased ventricular filling pressure, cardiac work as well as cardiac output increased in congestive heart failure, and that cardiac work and cardiac output both decreased in normal circulations. These hemodynamic changes are consistent with Starling's law.

Instaneous Measurement of Oxygen Saturation at Cardiac Catheterization Using Reflected Light

W. G. Zijlstra, G. A. Mook, Groningen, The Netherlands, and A. S. Nadas, Boston, Mass.

Most of the methods currently used for oximetry in the United States are based on measuring the light transmission of blood samples or tissues. A different approach was proposed by Brinkman and Zijlstra, who used light reflection instead of light transmission as an index of oxygen saturation. Reflection oximetry has the following advantages: 1. No hemolysis is needed. 2. Under ordinary circumstances and using certain precautions, the blood reflection is independent of the total hemoglobin concentration. 3. Relatively small light sources can be used.

The reflection principle found clinical application in the "haemoreflector," measuring oxygen saturation of blood samples. A second application is the "cyclops"-oximeter, which gives a continuous indication of changes in oxygen saturation through the intact skin.

Another application of reflection oximetry has been developed by having a cuvette directly connected to a cardiac catheter, giving the cardiologist the advantage of instantaneous determination of oxygen saturation in the individual cardiac chambers. The blood is drawn into a cuvette equipped with a magnetically driven mixing rod to break up rouleaus. After the zero point of the oximeter has been adjusted with an india ink filled cuvette, the oximeter is placed over the cuvette filled with blood. Galvanometer readings indicate the exact differences in oxygen saturation between individual samples. Absolute values may be obtained by determining the oxygen saturation of 1 sample of a series by a hemoreflector or other reliable method. Comparing the results yielded by this method with those obtained by hemoreflector or Beckman spectrophotometer reveal an accuracy adequate for clinical purposes.

Study of the Electrocardiogram During Open Heart Surgery with the Pump Oxygenator

Henry A. Zimmerman, Jorge Martins, and David Mendelsohn, Cleveland, Ohio.

In a series of 80 patients with a variety of anatomic defects who had open heart surgery with the Kay oxygenator, the electrocardiograms have been studied before, during, and after cardiac surgery. The following changes occur during and after surgery.

In the intra-atrial defects, the P axis tends to go leftward and backward. The R s R′ s′ pattern changes with disappearance or decrease in S′ wave. The right ventricular overload pattern decreased. In most patients, alteration in the R′S′ pattern in V_1 appears to be concerned with hemodynamic changes in the right ventricle and possible decrease in dilation and hypertrophy of the crista supraventricularis and other structures in the basal portion of the chamber wall and of the intraventricular septem.

In the intraventricular septal defects, the appearance of R′ or R′ S′ in V_1 are increased in these pat-

terns if they existed before. Widening of the S waves in lead 1 and the T waves become inverted in the precordial leads.

The suggestive delay in conduction probably is concerned with change of the basal portions of the septum and free wall of the right ventricle. These alterations were present in both groups of cases with and without pulmonary hypertension.

In the tetralogy of Fallot the following was noted: Decrease in R in V_1, appearance of R′ or R′ S′ waves, increased right axis deviation, appearance of widened S waves in lead 1 and greater R waves in a VR, and the T wave becomes negative in the precordial leads. These changes are similar as explained for intraventricular septal defects.

Indications and Contraindications for Open Heart Surgery

Henry A. Zimmerman, and Mohinder P. Sambhi, Cleveland, Ohio.

Surgical repair of various congenital cardiac defects has been carried out on 70 cases employing a total circulatory bypass. These cases included septal defects, pulmonic stenosis, patent ductus arteriosus, either in combination or as isolated lesions. Complete physiologic studies were carried out on all these cases preoperatively. On the basis of the experience gained, certain indications and contraindications for surgical repair of these lesions have become apparent.

In cases of ventricular septal defect, the data disclose that the closure of this defect is best tolerated at a time when these cases still have a dominant left-to-right shunt. This assessment is made by hemodynamic and electrocardiographic criteria to be presented. The ability of the pulmonary vasculature to respond to inhalation of 100 per cent O_2 and intracatheter aminophyllin coupled with the absence of microscopic changes of a severe grade of pulmonary arteriosclerosis in a frozen section of a lung biopsy taken at the time of thoracotomy immediately preoperative, correlated with the expectation of a good postoperative result. Most of the cases of intra-atrial septal defects did well if they had not developed reversed shunts and cyanosis. These changes being late and the technical advances still in progress, the criteria for earliest intervention may be more personal. We have regarded the addition of subjective symptoms to the hemodynamic, radiologic, and electrocardiographic criteria as indication for operation.

In cases of pulmonic stenosis, the height of right ventricular pressure more than 80 mm. of Hg, regarded as a contraindication for valvulotomy by some investigators, did not seem to hold true in our patients. In cases of tetralogy of Fallot, however, it seemed that the site and severity of pulmonic stenosis influenced the postoperative outcome and not the size of the ventricular septal defect or the position of the aorta.

The indications and contraindications for these procedures need further experience to be crystallized, yet it is important to attempt to arrive at certain accepted criteria for correct time of intervention for the interim stage of this rapidly progressing field.

Quinine and Quinidine Sulfate as Coronary Vasodilators

Burton L. Zohman, Brooklyn, N. Y., Henry I. Russek, Staten Island, N. Y., and Alice E. Drumm, Brooklyn, N. Y.

As far back as 1898, it was shown that quinidine and quinine have a vasodilating action in laboratory animals. Because of the inapplicability of animal observations in man and the inaccuracy of clinical estimates of coronary efficiency that are based on the symptom of pain, we decided to record the ability of quinine and quinidine to modify the ECG response to standard exercise (Master two-step test) in carefully selected cases. Only patients with coronary artery disease, who in repeated testing exhibited a relatively constant positive response to a given amount of exercise, were included. In addition, the control response could be favorably modified by the sublingual administration of therapeutic doses of nitroglycerin just before the test. By establishing this prerequisite, it was felt that a basis for comparison could be obtained between the effect of the potent coronary vasodilator nitroglycerin and that of quinine and quinidine sulfate. Two tests were performed in a single day. One and one-half and 3-hour studies were made on one day and 2- and 4-hour studies on the next. In a dose of 10 grains quinine sulfate was found to exert a "good" to "very good" modifying influence for as long as 4 hours on the ECG response to standard exercise in 6 of 14 patients tested. There was no response in 8 patients. Similarly, in a dose of 6 grains, quinidine sulfate was found to effect a "good" to "very good" response in 7 of 13 patients tested and for as long as 4 hours.

It would seem from this study that quinine and quinidine sulfate have the ability to modify favorably the electrocardiographic response to exercise (Master two-step test) and that quinidine does so somewhat better than quinine. Both have a coronary vasodilator action and should be effective agents in the treatment of angina pectoris.

MEDICAL MOTION PICTURES

DAILY PROGRAM

OCTOBER 25–27, 1957

October 25, Ruby Room **October 26-27, Old Chicago Room**

9:30 A.M. to 12:00 Noon

9:30 **William Harvey and the Circulation of the Blood** (Color, Sound)
Royal College of Physicians, Sir Henry Dale, London, England

10:15 **Open Operation for Aortic and Pulmonic Stenosis** (Color, Sound)
Henry Swan, M.D., Denver, Colo.

10:35 **Disorders of the Heart Beat** (Color, Sound)
American Heart Association, New York, N. Y.

10:55 **Tetralogy of Fallot** (Color, Sound)
John C. Jones, M.D., Los Angeles, Calif.

11:25 **Anatomic Correction of the Tetralogy of Fallot Defects under Direct Vision, Utilizing the Pump-Oxygenator** (Color, Sound)
C. Walton Lillehei, M.D., Minneapolis, Minn.

2:00 P.M. to 5:00 P.M.

2:00 **William Harvey and the Circulation of the Blood** (Color, Sound)
Royal College of Physicians, Sir Henry Dale, London, England

2:45 **Aortic Graft for Abdominal Aneurysm** (Color, Sound)
A. W. Humphries, M.D., Cleveland, Ohio

3:05 **Femoral Graft for Arteriosclerosis Obliterans** (Color, Sound)
A. W. Humphries, M.D., Cleveland, Ohio

3:25 **Movements of the Valves of the Heart and the Origin of the Heart Sounds** (Color, Combination of Silent and Sound)
H. E. Essex, M.D. and H. L. Smith, M.D., Rochester, Minn.

3:50 **Still Going Places** (Black and White, Sound)
Frederick D. Zeman, M.D. and Leo Dobrin, M.D., New York, N. Y.

4:30 **Hepato-Jugular Reflex** (Color, Sound)
J. Marion Bryant, M.D., New York, N. Y.

SCIENTIFIC EXHIBITS

Lower Exhibit Hall

Genetic Determination of Serum Cholesterol Level: Study of 201 Families. *David Adlersberg, Louis E. Schaefer, and Arthur G. Steinberg, New York, N. Y.*

Analysis of 201 families, 402 parents and their 373 children, totaling 775 individuals, selected at random from a group of employees of low-middle income. The frequency of hypercholesteremia was 17 per cent among the children who had a hypercholesteremic parent and 2 per cent among children of normocholesteremic parents. Correlation coefficients indicate that the serum cholesterol levels of fathers and mothers were unrelated, whereas the levels of the children were significantly associated with those of the parents and the levels of the siblings significantly related to each other. These data add evidence to the concept that serum cholesterol concentration at any level is genetically determined and that predisposition to atherosclerosis may be, at least in part, genetic in its nature.
(Booth I)

Use of a Sphere for the Analysis of Electrocardiac Entities in Space. *Louis Brinberg, New York, N. Y.*

Vectors are represented by points on the surface of a sphere and the method of determining these points is shown. A spatial angle equals the arc distance between two points. Normal values are demonstrated for electric axis, ventricular gradient, QRS-T angle and QRS-VG angle.
(Booth L)

Ventricular Septal Defect—Diagnosis and Surgical Treatment. *H. B. Burchell, R. O. Brandenberg, A. J. Bruwer, D. E. Donald, J. W. DuShane, J. E. Edwards, H. G. Harshbarger, J. W. Kirklin, H. J. C. Swan, and E. H. Wood, Rochester, Minn.*

It is important to recognize the varied clinical syndromes produced by ventricular septal defects now that surgical repair of these defects is being accomplished. These syndromes and their relation to the size of the ventricular septal defect and the magnitude of pulmonary resistance are illustrated and described. The pathologic anatomic features of ventricular septal defect, both as an isolated lesion and as part of the tetralogy of Fallot, are demonstrated by models. Roentgenologic, electrocardiographic and clinical features pertinent to the diagnosis of this malformation are depicted. Hemodynamic data are correlated with other observations in cases of ventricular septal defect. The technic for repair of ventricular septal defect by open cardiotomy while the patient is supported by a mechanical pump-oxygenator is shown. The results of surgical repair support the belief that operation is indicated for patients with large left-to-right shunts across ventricular septal defects.
(Booth Q)

Rapid and Reliable Screening Method for Detection of Heart Disease in Children. *Chicago Heart Association, United States Public Health Service, and Chicago Board of Health, Chicago, Ill.*

Studies using tape recording equipment modified by us have demonstrated that this method can be utilized in mass screening of school children for heart disease. This technic can record 50 children per hour with a high degree of accuracy as proven by statistical study of large numbers of recordings.
(Booth B)

Subminiature Intracardiac Manometer for Infants and Adults. *E. H. Drake, Detroit, Mich., and A. Warnick, Dearborn, Mich.*

The exhibit shows a functioning intracardiac manometer of hollow construction mounted on a No. 6 French catheter. Intracardiac manometry eliminates distortion created by pressure transmission through fluid columns. The new instrument faithfully records dynamic variations within the physiologic range. An enlarged model is presented showing construction details and representative pressure tracings are displayed.
(Booth H)

Evaluation of Arterial Reconstruction and Sympathectomy by Direct Stimulation Ergometry. *Edward A. Edwards, Boston, Mass.*

Electric stimulation of the calf muscles was employed in 48 limbs before and up to 3 years after operation to relieve ischemia. A measured average increase in power was maximal at 10 months after reconstruction and 13 months after sympathectomy. Instances of lack of improvement can be partly explained.
(Booth F)

Open Heart Surgery in Acquired Valvular Disease. *Earle B. Kay, Frederick S. Cross, and Henry A. Zimmerman, Cleveland, Ohio.*

The exhibit will deal with the indications and contraindications to open heart surgery and acquired valvular disease. The technical aspects essential to left sided cardiotomies will be emphasized. Surgical and pathological illustrations of the types of acquired valvular disease amenable to surgery will be presented as well as the morbidity factors and results. A movie illustrating many of these aspects also will be incorporated into the exhibit.
(Booth A)

Evaluation of C-Reactive Protein and SGO Transaminase in Coronary Artery Disease. *Irving G. Kroop and Nathan H. Shackman, Brooklyn, N. Y.*

The C-reactive protein test is more sensitive than the transaminase test in the diagnosis of the milder case of myocardial necrosis but cannot be used unless all extracardiac stimuli for its formation are absent. The transaminase level is not diagnostic in these cases because insufficient enzyme is released to elevate the serum concentration beyond the normal range (29 out of 45 cases).
(Booth M)

Timed Vital Capacity. *C. M. Kurtz and J. K. Curtis, Madison, Wis.*

Timed vital capacity (TVC) differentiates between restrictive and obstructive types of breathing. Hence this test is helpful in distinguishing asthmatic bronchitis and cardiac asthma. In cardiac decompensation the vital capacity (VC) is reduced and improves with establishment of compensation. A simple spirometer apparatus will demonstrate how records of VC and TVC may be made on the electrocardiograph.
(Booth C)

Anisindione—New Improved Anticoagulant. *Kurt Lange, Murray M. Mahl, Eli Perchuk, and Joseph Enzinger, New York, N. Y.*

Anisindione, an oral anticoagulant of the indandione type, elicits predictable and rather uniform effects with a given dose. Its action is prompt and sustained. A smooth curve of hypoprothrombinemia is obtained with a maintenance dose every third day. The required dosage varies very little from case to case. To produce undesirably low prothrombin activity excessively large doses of anisindione are required.
(Booth P)

Influence of Cardiopulmonary Bypass Procedures on Cardiac Contractility and Sympathoadrenal Function. *Wm. H. Lee, Jr., Thomas D. Darby, Eugene F. Woods, J. D. Ashmore, James A. Richardson, and Edward F. Parker, Charleston, S. C.*

Direct measurements of changes in the force of contraction of the ventricular musculature were used for the early detection of disturbances in cardiac function secondary to cardiopulmonary bypass procedures. Evidence is presented that serious deficiencies in cardiac contractility may occur when the electrocardiogram, arterial pressure, etc. are essentially unchanged. Participation of the sympathoadrenal system has been evaluated by measuring plasma concentrations of epinephrine and arterenol.
(Booth G)

Controlled Study on the Prevention of Streptococcal Infection and Rheumatic Fever with Penicillin. *Benedict F. Massell, Samuel L. Stancer, Joseph M. Miller, John A. Vecchiolla, Sidney Brodie, and Eliot Young, Boston, Mass.*

The relative advantages and disadvantages of oral buffered penicillin G, oral penicillin V, and intramuscular benzathine penicillin G for preventing streptococcal respiratory infection (and rheumatic fever) are demonstrated. Effectiveness is measured by comparing the incidence of streptococcal infection among rheumatic subjects, given penicillin, and among their siblings, not given penicillin.
(Booth J)

Pulmonary Hypertensive Cardiovascular Disease. *Thomas W. Mattingly, Loren F. Parmley, Jr., and Robert J. Hall, Washington, D. C.*

The exhibit presents a classification of pulmonary hyperentsive cardiovascular disease and depicts the incidence as encountered during a 6-year clinical study, including over 500 right heart catheterizations. The clinical, hemodynamic, and pathologic features of the primary and secondary forms of the disease are demonstrated with emphasis on the distinguishing features of each. Current ideas as to pathogenesis and approaches to therapy are also presented.
(Booth D)

Encouraging News about Strokes. *National Heart Institute and Heart Disease Control Program, Public Health Service, Bethesda, Md.*

Hope and help for people who have suffered strokes is the keynote of a Public Health Service exhibit, poster, and booklet designed for use by physicians and other professional persons to promote better understanding of cerebral vascular disease and strokes among patients, their families, and the general public.
(Booth S)

Strokes Caused by Diseases of the Heart and Aorta. *T. W. Parkin, C. H. Millikan, G. P. Sayre, and J. E. Edwards, Rochester, Minn.*

Considerable interest has developed recently concerning the problem of strokes. In most instances, strokes are associated with primary disease of cerebral arteries, but they may be caused at times by certain diseases of the heart or aorta. Such strokes may result from (1) cerebral ischemia caused by decreased cardiac output, (2) cerebral embolism or (3) cerebral hemorrhage. This exhibit portrays with models and photographs the important diseases of the heart and aorta that may produce strokes. The chief clinical manifestations of strokes occurring as complications of cardiac diseases and the underlying pathologic changes in the brain are illustrated.
(Booth N)

Prevention of Rheumatic Fever. *Rheumatic Fever Prevention Sub-Committee, Chicago Heart Association, Chicago, Ill.*

The exhibit will emphasize the management of streptococcal infections in private practice, including

live demonstrations of practical throat-culturing technics. Material on primary, as well as secondary, prevention will be available. A portable laboratory for the purpose of taking throat cultures on the spot will be a part of the exhibit.
(Booth T)

Disposable Oxygenator with Low Priming Volume. *Peter F. Salisbury, Los Angeles, Calif.*

A plastic disposable oxygenator will be shown which can arterialize 1,200 to 1,500 ml. blood per minute and which requires only 200 to 300 ml. priming blood. It is primarily intended as an auxiliary circulation in patients with intractable heart failure, but can also be used for open heart surgery.
(Booth O)

Left Transventricular Approach to the Aortic and Mitral Valves and to the Interventricular Septum. *Victor P. Satinsky, Eugene V. Kompaniez, Robert Kuhn, and Richard N. Baum, Los Angeles, Calif.*

After bypassing the heart and lungs by means of a pump-oxygenator, easy access to the interventricular septum, the annulus of the aortic valve and the leaflets of the mitral valve may be obtained. Either retrograde coronary artery perfusion or induced cardiac arrest may be employed as an adjunct to the procedure.
(Booth R)

Timed Vectorcardiogram. *Ronald H. Selvester and Donald E. Griggs, Los Angeles, Calif.*

The spatial vectorcardiogram graphically portrays vector forces. However, P, QRS, and T are often superimposed; time relationships are hard to evaluate; rate, PR, and QT intervals are not recorded. Electrocardiograms depict more clearly time relationships of cardiac cycle. The timed vectorcardiogram combines advantages of each into simplified graphic method.
(Booth K)

American Heart Association

Information booth and display of materials for the physician.
(Booth E)

TECHNICAL EXHIBITS

Main Exhibit Hall

Arlington Medical Company, Arlington Heights, Ill. (Booth 22).

Baxter Laboratories, Inc., Morton Grove, Ill. (Booth 65), *presents Sera-Vac—the only blood bottle with the internal pilot tube—prevents errors, saves time. Transfuso-Vac for better platelet preservation. Plexitron Sets for simpler blood collection and transfusion. The R-48 Blood Administration Set provides for both Gravity blood transfusion and safe Pressure transfusion procedures.*

Beck-Lee Corporation, Chicago, Ill. (Booth 14). *World's largest exclusive manufacturer of EKG's, will display their Cardi-all Direct Writing EKG. This instrument features full-scale performance, extreme simplicity of operation, life-time standardization, light-weight portability, and rugged construction. Cardi-all is housed in a solid-mahogany cabinet which contributes to its outstanding modern appearance.*

Bowen & Company, Inc., Bethesda, Md. (Booth 64). *Actual demonstrations of our accurately Calibrated Ballistocardiograph, Smith-Perls Model, will be presented. Additional products displayed will be: Welsh Self-Retaining Electrodes, QU Calculator for determining the QTc or the QT Ratio, Bowen Liquid Dispenser for alcohol and other cleansing liquids. Newest item will be the Krasno-Graybiel Metal Plastrodes: a metal and plaster electrode requiring* no *electrode paste (jelly).*

Brewer & Company, Inc., Worcester, Mass. (Booth 17). *This exhibit consists of specialties centering around Thesodate, the original enteric-coated tablet of theobromine sodium acetate, and includes our newer products: R-S-Thesodate, which is a combination of Thesodate and Rauwolfia serpentina whole powdered root; and Rauwolfia serpentina tablets 50 and 100 mg. Also featured are: Amchlor, enteric-coated, 1 Gm. tablets of ammonium chloride; Enkide, enteric-coated tablets of potassium iodide; Gel-Ets, the newest mode in oral vitamin therapy; and Soduxin (sodium succinate-Brewer) ampuls. Literature will be available on Injectable Quinidine Hydrochloride (original injectable quinidine product on the American market for both intravenous and intramuscular use), and Sus-Phrine (aqueous suspension of epinephrine 1:200—Brewer) for subcutaneous injection in the treatment of bronchial asthma.*

Burdick Corporation, Milton, Wis. (Booth 35), *will display their latest models of electrocardiographic equipment. Burdick customers are invited to stop by their booth to make or renew acquaintance. Those not familiar with the Burdick Electrocardiograph are invited to see it in operation. Members of their sales and engineering staff will be there to greet you.*

Burroughs Wellcome & Company (U. S. A.) Inc., Tuckahoe, N. Y. (Booth 71). *The extensive research facilities of B. W. & Co., both here and in other countries, are directed to the development of improved therapeutic agents and technics. Through such research they have made notable advances related to leukemia, malaria, diabetes, and diseases of the autonomic nervous system, and to antibiotic, muscle-relaxant, antihistaminic, and antinauseant drugs. An informed staff at their booth will welcome the opportunity to discuss their products and latest developments with you.*

Cambridge Instrument Company, Inc., New York, N. Y. (Booths 45 and 46). *The Cambridge Audio-Visual Heart Sound Recorder; the well-known Cambridge "Simpli-Scribe" Model Direct-Writing Portable Electrocardiograph and the Cambridge Standard String Galvanometer Electrocardiograph, both in the "Simpli-Trol" Portable and the Mobile Model Electrocardiograph-Stethograph with Pulse Recorder, will be displayed. Also other important Cambridge instruments, including the Operating Room Cardioscope, Educational Cardioscope, Multi-Channel Direct-Writing Recorder, Catheterization Monitor-Recorder, Electrokymograph, Plethysmograph, pH Meters and Respiratory Gas Analysers. The Cambridge Engineers in attendance will be glad to give you complete information on these instruments.*

Carnation Company, Los Angeles, Calif. (Booth 49) *welcomes friends of long standing as well as new members. At their booth, a refreshing drink of Carnation Instant Nonfat Milk will be served. Carnation representatives will be pleased to discuss with you the physician-researched material for use in your practices as a service of their company.*

Coca-Cola Company, Atlanta, Ga. *Ice-cold Coca-Cola will be served through the courtesy and cooperation of The Coca-Cola Company.*

Colson Corporation, Elyria, Ohio (Booth 59). *The Colson Densitometer used in the determination of cardiac output by the dye-dilution method will be demonstrated on a model of the circulation. Actual output curves will be recorded, using the newly developed constant velocity hypodermic syringe actuator to draw fluid through the cuvette. Also in operation will be Colson's Automatic Sphygmomanometer, periodically recording diastolic and systolic pressure on an unattended subject.*

Dallons Laboratories, Inc., Los Angeles, Calif. (Booth 9), *will display their new 1958 Cardioscope and demonstrate its operation for continuous monitoring of cardiac potentials during surgery. The Dallons CP-3-6 Cardiophone will also be demonstrated. The Cardiophone produces clear and distinct sound translation of the heart muscle potentials. Any deviation from normal heart rhythm or electric potentials is immediately discernible. The Cardiac Defibrillator and Cardiac Pacer will also be shown. Competent factory representatives will be on hand to answer your questions and you are cordially invited to visit their booth.*

Darwin Laboratories, Los Angeles, Calif. (Booth 2). *Lipo-Hepin 200; sodium heparin U.S.P. in purified form allowing only 1 or 2 injections per day for 24-hour anticoagulant effect, regardless of patient weight. Ready to use, no prewarming, convenient, economical and effective. Dar-Zyme: purified trypsin with antibiotic in ointment form for topical proteoplytic digestion of necrotic tissue. Ready to use, economical, convenient and effective. Adrenalex-Geriatric: Hormone (estrogentestosteron), vitamin and hemotopoietic combination capsule for use in treatment and prevention of certain geriatric problems.*

Davies, Rose & Company, Ltd., Boston, Mass. (Booth 68). *A cordial invitation is extended to the members to visit their booth. Although most physicians need no introduction to their outstanding cardiac therapies—Pil. Digitalis and Tablets Quinidine Sulfate (Natural)—our representatives, Messrs. H. V. Orne and W. Earle Purinton, will be present to welcome you and to explain the dependability of their laboratory productions.*

F. A. Davis Company Medical Publishers, Philadelphia, Pa. (Booth 67). *The new Looseleaf Edition of Stroud & Stroud:* Cardiovascular Disease *will be shown for the first time at the American Heart Association meeting. Sixty outstanding authorities in cardiology have contributed new and revised chapters in the foremost postgraduate presentation of Cardiology available today. See also Simon:* Chest X-Ray Diagnosis *and a preview of Glasser:* Peripheral Vascular Surgery.

Electrodyne Company, Inc., Norwood, Mass. (Booth 42). *On display will be the latest instruments for closed chest detection and treatment of cardiac arrest and ventricular fibrillation. Featured will be the Electrodyne PM-65 with Electrocardioscope, which reliably monitors cardiac activity and automatically provides effective external stimulation of the dormant heart at the very onset of cardiac arrest. The PM-65 combines the popular Cardiac Monitor and the well-documented Electrodyne Cardiac Pacemaker into 1 versatile unit.*

Electronics For Medicine, Inc., White Plains, N. Y. (Booth 47). *A new 8-channel research recorder provides both scalar and loop tracings with an improved cathode ray camera. Cardiovascular and respiratory pressures, electrocardiogram, electroencephalogram, phonocardiogram and oxygen saturation can be recorded along with polarographic measurements, integrals, derivatives, and pressure gradients. The Cardiology Teaching Aid permits simultaneous tape recording for phonocardiogram and electrocardiogram or pulse wave, with visual and aural examination and permanent tracings.*

Encyclopaedia Britannica, Chicago, Ill. (Booth 21). Encyclopaedia Britannica *proudly announces the release of a brand new edition. Thirteen years of intensive editorial effort, representing an investment of more than five million dollars is reflected in this New Edition. You are cordially invited to inspect the finest* Britannica *ever published and to avail yourselves of the most sensational offer savings-wise ever made.*

Evron Company, Inc., Chicago, Ill. (Booth 32). *Pentritol Tempules for continuous 24-hour treatment of angina pectoris are presented. The significance of the 12 hours of coronary vasodilation produced by each 30 mg. capsule of PETN is substantiated by actual use. Since its introduction over 2 years ago, Pentritol has gained the support of clinical studies and office experience to establish its effectiveness. Prescribing 1 Tempule every 12 hours has been consistently valuable in controlling anginal spasms. Professional Representatives available to offer service, samples and literature.*

C. B. Fleet Company, Inc., Lynchburg, Va. (Booth 69). *Fleet will introduce Clysmathane, a coronary vasodilator and bronchodilator. Administration is by a new and simple method.*

Geigy Pharmaceuticals, Division of Geigy Chemical Corporation, Yonkers, N. Y. (Booth 62). *The Geigy exhibit will feature Preludin—the new chemically different appetite suppressant noted for its absence of side actions. Also on display will be Butazolidin—potent nonhormonal antiarthritic; new Sterosan hydrocortisone ointment—anti-inflammatory, bacteriostat and fungistat, and other well-known Geigy products.*

Grass Instrument Company, Quincy, Mass. (Booth 7). *Direct Recording Polygraph Model 5 will be exhibited. This versatile instrument is designed to measure neurologic and circulatory functions, including EEG, EKG, EMG, respiration, pressure, plethysmography O_2, CO_2, PGR. The application is in the operating room, clinic, laboratory, and class room.*

Gray Pharmaceutical Company, Inc., Newton, Mass. (Booth 23). *Atheroxin, the only corn oil-pyridoxine emulsion for the reduction of cholesterol will be exhibited. Atheroxin combines the cholesterol lowering factors of corn oil with pyridoxine hydro-*

chloride, a singularly effective agent for the utilization of essential unsaturated fatty acids. Atheroxin may be used to reduce serum cholesterol in patients with coronary artery disease and other conditions which exhibit an elevated cholesterol.

Grune & Stratton, Inc., Medical Publishers, New York, N. Y. (Booths 40 and 41). *Grune & Stratton invites you to examine* Circulation *and* Circulation Research *with our Mr. Frank Kurzer, and also such recent books as: Askey:* Arterial Embolism; *Alpers:* Dizziness; *Gordon:* Clinical Cardiopulmonary Physiology; *Redisch:* Peripheral Circulation in Health and Disease; *Scherf and Boyd:* Cardiovascular Diseases, *third revised edition; Sigler:* The Electrocardiogram, *second revised edition; Kossmann:* Progress In Electrocardiography, *and other valuable works for the practicing physician in internal medicine.*

Paul B. Hoeber, Inc., New York, N. Y. (Booth 3). *Here you will be able to examine 4 new and important books published this year: Plotz'* Coronary Heart Disease, *Gardberg's* Clinical Electrocardiology, *Naclerio's* Bronchopulmonary Diseases, *and Bayley's* Biophysical Principles of Electrocardiography, *just coming off press. All books on the Hoeber-Harper list will be available, and you are invited to browse at leisure.*

Industrial Acoustics Company, Inc., New York, N. Y. (Booth 26). *will display material showing the use of an I.A.C. Series "1200" soundproof room for research of heart sounds and auscultation. These rooms are designed and engineered to provide the ultimate in acoustical performance. The features which make these rooms unique in their field will be pointed out.*

Lea & Febiger, Philadelphia, Pa. (Booth 1), *welcomes you to their booth where you can examine such books as Katz and Pick*—Clinical Electrocardiography; *Master, Moser and Jaffe*—Cardiac Emergencies and Heart Failure; *Goldberger*—Heart Disease; *Burch and Winsor*—Primer of Electrocardiography; *Burch*—Primer of Cardiology; *Goldberger*—Unipolar Lead Electrocardiography; *Pratt*—Cardiovascular (Artery and Vein) Surgery; *and many others.*

Lederle Laboratories, Division of American Cyanamid Company, Pearl River, N. Y. (Booth 15).

Thos. Leeming & Company, Inc., New York, N. Y. (Booth 36). *The use of Metamine (triethanolamine trinitrate biphosphate) in the prevention of angina pectoris will be presented. The b.i.d. dosage form of this drug, Metamine Sustained, will be featured, and physicians who are not familiar with this unique cardiac nitrate are urged to visit our booth, where comprehensive literature will be available.*

Eli Lilly and Company, Indianapolis, Ind. (Booths 5 and 6). *You are cordially invited to visit the Lilly exhibit. Sales people in attendance welcome your questions about Lilly products and recent therapeutic developments.*

Macmillan Company, New York, N. Y. (Booth 44). *The Macmillan Company will have on display some well-established, as well as several new, titles in the cardiology field. Of special interest will be Briskier:* Cardio-Charting: Universal Method of Recording Heart Auscultation, *and Keith-Rowe-Vlad:* Heart Disease in Infancy and Childhood.

Maico Company, Inc., Minneapolis, Minn. (Booth 52), *will show their amplifying electronic stethoscope, the Maico Stethetron. By means of filters this instrument will permit one to concentrate on the low-pitched heart murmurs while screening out the higher-pitched tones. Experienced personnel will be on hand to give you a demonstration.*

Mark Company, Randolph, Mass. (Booth 37). *Introducing for the first time in this country, universally accepted famous Schwarzer Electrocardiographs, employing from 1 to 16 channels. Also, all stainless steel, completely autoclavable, Cooley Mechanical Heart-Lung and Clowes Membrane Oxygenator, in addition to explosion-proof Heart Defibrillator, and Gibbon-type Mark GK Mechanical Heart-Lung Apparatus.*

Merck Sharp & Dohme, Division of Merck & Company, Inc., Philadelphia, Pa. (Booth 34). *Their exhibit highlights steroid therapy featuring new adrenal cortical steroid preparations—Meprolone, Hydeltra-T.B.A., and Neo-Hydeltrasol. New antibacterial agents of clinical significance are also featured. Technically trained personnel will be present to discuss these and other subjects of clinical interest.*

C. V. Mosby Company, St. Louis, Mo. (Booth 11). *You are cordially invited to visit their booth, where you will find displayed the following new books and new editions. Sodi-Pallares* New Bases of Electrocardiography, *Myers* Interpretation of the Unipolar Electrocardiogram, *Meakins* Practice of Medicine, *Bard* Medical Physiology, *Anderson* Pathology, *Lisser-Escamilla* Atlas of Clinical Endocrinology, *and Williamson* Practical Use of Office Laboratory and X-Ray (including the Electrocardiograph).

Nepera Laboratories Division, Morris Plains, N. J. (Booth 16). *Their exhibit features a new xanthine drug, Choledyl, which has proven highly effective and well tolerated when used orally as a prophylactic agent in chronic emphysema and bronchial asthma. Its mild diuretic action makes it useful as an oral nonmercurial diuretic in the treatment of congestive heart failure. The representatives at their booth welcome inquiries regarding this new and unique agent, and*

are prepared to discuss a recent controlled study demonstrating the effectiveness of Choledyl in preventing the recurrence of anginal attacks.

North American Philips Company, Inc., New York, N. Y. (Booth 12). *Reflecting the ever-increasing interest in this comparatively new technic, their display will consist of the 5" Philips Image Intensifier with 3 separate viewing systems; a mirror viewer, cineradiographic hook-up and a closed circuit television execution, the 11" Philips Image Intensifier designed primarily for cineradiographic studies.*

Pet Milk Company, St. Louis, Mo. (Booth 60). *They will be pleased to have you stop and taste the "fresh milk flavor" of Instant "Pet" Nonfat Dry Milk. Their representatives will be on hand to serve you and discuss the use of Instant "Pet" Nonfat Dry Milk in special diets.*

Raytheon Manufacturing Company, Waltham, Mass. (Booth 50).

Riker Laboratories, Inc., Los Angeles, Calif. (Booth 43). *Their exhibit features its list of pioneering firsts: Rauwiloid (alseroxylon) and its combinations in the management of hypertension; Pentoxylon in angina pectoris; the new highly effective skeletal muscle relaxant, Disipal, for relief of muscular spasm in backache, injuries, arthralgias and Parkinsonism. Also featured is Medihaler-Epi and Medihaler-Iso, measured-dose aerosol nebulization for effective asthma control.*

Sanborn Company, Waltham, Mass. (Booths 29 and 30). *Visitors at their booth will have full opportunity to see and have demonstrated our continually expanding line of equipment for biophysical diagnosis, teaching and research. Instrumentation to be shown or described will include single and multi-channel recording systems—direct-writing, photographic and tape; supplementary oscilloscopes; and physiologic transducers of several types. Workers in the cardiovascular and other research fields should not miss the opportunity to examine this varied equipment, and to discuss with our engineers its applicability to their investigative problems.*

Sandoz Pharmaceuticals Division, Hanover, N. J. (Booth 66). *You are cordially invited to visit their display: Acylanid has all the advantages of digitoxin but has the safety of the whole leaf digitalis. Cedilanid pure glycoside (lanatoside C) of digitalis lanata with quick onset of action, quick excretion, low toxicity useful for i. v. administration in cardiac emergencies. Their representatives will gladly answer questions about this and other Sandoz products.*

Instant Sanka Coffee, White Plains, N. Y. (Booths 72 and 73). *You are invited to stop by their booths for a cup of Instant Sanka, a hearty coffee. Sanka is pure coffee, 97 per cent caffein-free . . . there isn't a jitter in a jarful. Do try Instant Sanka, and while at their booth, register for professional samples and booklets.*

W. B. Saunders Company, Philadelphia, Pa. (Booth 63). *Current Saunders titles of special interest to physicians in heart work include: Nadas:* Pediatric Cardiology; *Rodriguez:* An Atlas of Cardiac Surgery; *and Friedberg:* Diseases of the Heart.

Schering Corporation, Bloomfield, N. J. (Booth 31). *Members of the Association and guests are cordially invited to visit the Schering exhibit where new therapeutic developments will be featured. Their representatives will be present to welcome you and to discuss with you the various products they manufacture.*

Schieffelin & Company, New York, N. Y. (Booth 33).

G. D. Searle & Company, Chicago, Ill. (Booth 8). *You are cordially invited to visit their booth where representatives will be happy to answer any questions regarding their various products of research. Featured will be Nilevar, the new anabolic agent; Rolicton, the new safe, non-mercurial oral diuretic; Vallestril, the new synthetic estrogen with extremely low incidence of side reactions; Banthine and Pro-Banthine, the standards in anti-cholinergic therapy; and Dramamine, for the prevention and treatment of motion sickness and other nauseas.*

Sherman Laboratories, Detroit, Mich. (Booth 56). *When therapeutic theophylline blood-levels are achieved, the myocardium is strengthened, bronchioles and peripheral blood vessels are relaxed, venous pressure is lowered, circulation time is shortened and coronary and pulmonary circulations are increased. Hitherto, these effects were reliably available only with parenteral therapy. Now, these clinically valuable properties of theophylline are dependably secured by the oral route—with Elixophyllin.*

E. R. Squibb & Sons, New York, N. Y. (Booth 13), *has long been a leader in development of new therapeutic agents for prevention and treatment of disease. The results of their diligent research are available to the medical profession in new products or improvements in products already marked. At their booth, they will be pleased to present up-to-date information on these advances for your consideration.*

Statham Laboratories, Inc., Los Angeles, Calif. (Booth 53). *Four types of Statham unbonded strain gage manometers intended especially for biologic measurements will be displayed by experienced engineering personnel. These 4 models of Statham pressure transducers have found wide acceptance in*

the field of cardiac catheterization because of their inherent stability, excellent dynamic response and simplicity of operation.

R. J. Strasenburgh Company, Rochester, N. Y. (Booth 48). *New Biphetamine, providing a more satisfactory means of controlling body weight where indicated, is featured. Clinicians report an average weight loss characteristic of 2 to 3 lbs. per week in nearly all cases of obesity due to excessive eating. Predictable sustained ionic release assures 10- to 12-hour appetite suppression without discomfort or disturbance of normal sleeping habits. For details, visit their booth.*

Charles C Thomas, Publisher, Springfield, Ill. (Booth 70). *Some of the books they will display for the first time are: Edwards*—Plastic Arterial Grafts; *Gasul, et al.*—Angiocardiography in the Diagnosis of the Cyanotic Types of Congenital Malformations of the Heart; *Lamb*—Electrocardiography and Vectorcardiography; *Rinzler*—Clinical Aspects of Arteriosclerosis; *Rabin*—Roentgenology of the Chest *sponsored by the American College of Chest Physicians; Schroeder*—Mechanisms of Hypertension.

U. S. Vitamin Corporation, New York, N. Y. (Booth 39). *New—on display—Arlidin, the safe vasodilator drug with 3 unique pharmacologic actions: (1) dilates predominantly small blood vessels of skeletal muscle, (2) increases cardiac output without significant increase in pulse rate, (3) promotes greater circulating blood volume. Thus, Arlidin (Nylidrin HCl. NNR) is indicated in treating intermittent claudication in arteriosclerosis obliterans, thromboangiitis obliterans, and diabetic vascular disease; also effective in Raynaud's Syndrome and ischemic ulcers. Professional samples and literature distributed also on their complete line of nutritional and pharmaceutical specialties.*

Varick Pharmacal Company, Inc., Hicksville, N. Y. (Booth 57). *Digitaline Nativelle Intramuscular, the only parenteral digitoxin designed specifically for intramuscular injection will be described. Indicated when the oral route is unavailable. Digitaline Nativelle Intramuscular exerts the identical response of oral or intravenous Digitaline Nativelle, both as to speed of action and therapeutic effect. Clinical supplies for evaluation will be available on request.*

Walker Laboratories, Inc., Mt. Vernon, N. Y. (Booth 10). *At their booth, the feature product being exhibited is: Hedulin (PID), the oral anticoagulant of choice Ref. 1. Breneman, C. M. et al: Am. Heart J., July '55. Full details pertaining to the drug and reprints of all medical papers are available in complete portfolio form.*

Warner-Chilcott Laboratories, Morris Plains. N. J. (Booth 25). *Peritrate—Warner-Chilcott Laboratories feature Peritrate Sustained Action, a new dosage form of the long-acting coronary vasodilator, Peritrate. For the first time the angina patient is provided with around-the-clock protection against attack. Peritrate is effective in 4 out of 5 cases. Improved E. K. G. readings, and increased exercise tolerance offer objective evidence of Peritrate's effectiveness in angina.*

Waters Corporation, Rochester, Minn. (Booth 38), *will demonstrate its self-developing photokymograph recorder in combination with matching "modular control" system for simultaneous recording of multiple cardiopulmonary phenomena monitored by a 17-inch screen oscilloscope. Also featured will be a new, stable nitrogen gas analyzer, oximeter, cardiotachometer, and a thermistor offering extra sensitive, fast probes.*

Winthrop Laboratories, New York, N.Y. (Booth 20). *Isuprel (Ampuls and Glossets) for heart block, Adams-Stokes syndrome, cardiac standstill, carotid sinus hypersensitivity, and cardiac arrhythmias. In the management of these conditions, Isuprel has the unique advantage of stimulating and stabilizing the active ventricular pacemaker of the heart without inciting lower potential ventricular foci. Therefore, Isuprel in contrast to epinephrine, does not predispose the heart to ventricular fibrillation or tachycardia.*

Wyeth Laboratories, Philadelphia, Pa. (Booths 27 and 28), *will feature: Bicillin Injection (benzathine penicillin G) long-acting penicillin compound, valuable in rheumatic fever prophylaxis. Pen-Vee-Oral (penicillin V) new acid-stable oral penicillin which produces high blood levels. Sparine (promazine hydrochloride) potent ataractic drug, indicated in management of acutely agitated patients. Equanil (meprobamate) unique antianxiety agent with marked muscle-relaxing properties. Ansolysen (pentolinium tartrate) effective oral ganglionic blocking agent for management of hypertension. Thiomerin Sodium (mercaptomerin sodium) Injection and Rectal Suppositories, mercurial diuretic, virtually free of local or systemic toxicity.*

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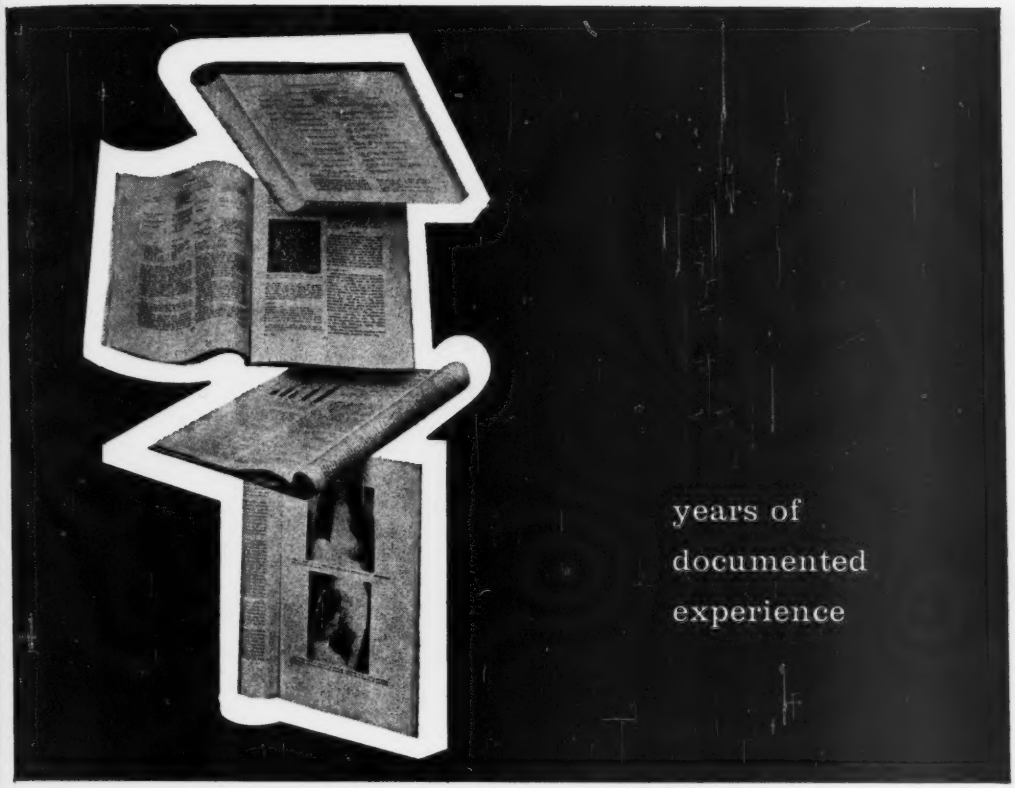

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